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THE BLOOD-CEREBROSPINAL FLUID BARRIER IN TUBERCULOUS MENINGITIS AND ALLIED CONDITIONS

BY

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The fact that many substances naturally present in blood, or artificially introduced into the bloodstream, either do not penetrate the central nervous system or do so only in small amounts has given rise to the concept of the " blood-brain barrier ". Some workers believe that this term is an oversimplification : they maintain that while certain dyes pass freely from blood to nervous tissue without appearing in the cerebrospinal fluid (C.S.F.), others can pass from blood to C.S.F. without penetrating the parenchyma of the brain. The presence of two barriers, a blood-brain and a blood-C.S.F. barrier, has therefore been postulated (Friedman, 1942). But whatever the relationship between the two barriers, if indeed they are distinct, the study in man of the passage of different substances from blood to nervous tissue is a matter of great practical difficulty. On the other hand, study of the partition of substances between blood and C.S.F. is relatively easy, and the chief technical difficulty lies in the choice of a suitable indicator substance. The present study is concerned solely with the passage of substances from blood to C.S.F. ; that is to say, with the blood-C.S.F. barrier.

One substance that has proved eminently suitable for studies of this kind is sodium bromide (Walter, 1929). The validity of the bromide test as a measure of the permeability of the blood-C.S.F. barrier has now been demonstrated (Hunter, Smith, and Taylor, 1954). Results of the test are expressed as the " bromide ratio ", that is to say, bromide per unit volume serum/bromide per unit volume C.S.F. In subjects without overt disease of the nervous system the bromide ratio at equilibrium varies between 1·95 and 3·39, with a mean of 2·6 and a standard deviation of 0·30 (Taylor, Smith, and Hunter, 1954).

It is commonly held that inflammation of the leptomeninges facilitates the passage of many substances from blood to C.S.F. Yet in spite of a great deal of work on both man and animals (Katzenelbogen, 1935) the exact effect of leptomeningitis on the permeability of the blood-C.S.F. barrier is still poorly understood : witness the controversy that persists over the necessity or otherwise of intrathecal medication in the treatment of meningitis (Smith, Duthie, and Cairns, 1946 ; Hoyne and Brown, 1948 ; Dowling, Sweet, Robinson, Zellers, and Hirsh, 1949 ; Smith, 1951). As the bromide test is both simple and safe, it provides a highly convenient method for studying the behaviour of the blood-C.S.F. barrier in inflammatory conditions of the nervous system. We have used it now in a large number of cases of tuberculous meningitis and also at different stages of the disease in the same case. We have also made serial estimations of the bromide ratio throughout the course of the intrathecal tuberculin reaction as seen in subjects in whom the meninges were otherwise normal. By the intrathecal tuberculin reaction is meant that wave of sterile meningitis which follows the introduction of tuberculin into the C.S.F. of someone sensitized to tuberculin (Smith and Vollum, 1950). Since in the absence of tuberculous meningitis this reaction is remarkably regular in both occurrence and pattern, it provides an excellent medium for studying the effects of meningeal inflammation on the permeability of the blood-C.S.F. barrier to any given test substance.

Methods

Full details of the bromide test have already been published (Taylor and others, 1954), but may be recapitulated here.

Sodium bromide may be given either by mouth or by intravenous injection. The oral dose for adults is 1 g. of sodium bromide three times a day for three days. Children receive a total dose of 2·25 to 4·5 g., depending on age, also given in divided doses. The intravenous dose for adults is from 6 to 8 g. and for children from 2 to 4 g., made up as a 25% solution in sterile water and given as a single injection. This solution is moderately irritating, and care must be taken to ensure that

* While working with a grant from the Medical Research Council.
† Now in receipt of a grant from the Nuffield Foundation, but at the time when the main part of the work reported in this paper was carried out was a member of the Medical Research Council's Electromedical Research Unit at Stoke Mandeville Hospital.

it is all delivered directly into the vein and none allowed to escape into the surrounding tissues.

At least 48 hours must elapse after the last oral dose, and 24 hours after the intravenous injection, in order to ensure that equilibrium is established between blood and C.S.F. Samples are then collected into chemically clean, dry test tubes. Bromide estimations are carried out on the serum and C.S.F. by the method described by Hunter (1953). Five ml. of blood and 1 ml. of C.S.F. is enough to allow the estimation to be done in duplicate. Bromide is excreted so slowly that the doses advised are sufficient to maintain measurable levels in the blood and C.S.F. for several weeks.

When penicillin was used as an indicator substance 500,000 u. was given by intramuscular injection approximately two hours before each lumbar puncture. The penicillin content of the C.S.F. was estimated and the results were expressed as the amount of penicillin present in 1 ml. C.S.F. and not as the blood-C.S.F. ratio.

The Bromide Ratio during the Intrathecal Tuberculin Reaction

When the intrathecal tuberculin reaction is provoked in subjects with normal meninges it follows a reasonably constant and characteristic pattern (Swithinbank, Smith, and Vollum, 1953). As with the intradermal tuberculin reaction, its intensity is the resultant of the quantity of tuberculin given and the sensitivity of the recipient. In its complete form the reaction is diphasic and consists of an initial wave of pleocytosis which is predominantly polymorphonuclear and is accompanied by an abrupt rise in the protein content of the C.S.F. This, the polymorphonuclear phase, is maximal about 24 hours after the injection and is succeeded by a second wave of pleocytosis which is entirely lymphocytic. The second phase is maximal between the fifth and eighth days of the reaction and is usually accompanied by a second peak in the protein curve. When the reaction is incomplete, either the first, polymorphonuclear, or, more commonly, the second, lymphocytic, phase is lacking and the rise in protein content is inconspicuous.

The effect of the reaction on the blood-C.S.F. barrier has been studied, using either penicillin or sodium bromide or both simultaneously, as indicators. The results obtained with penicillin have already been described. It was shown that whereas the first, polymorphonuclear, phase had little effect on the passage of penicillin from blood to C.S.F., the second, lymphocytic, phase of the reaction was accompanied by a well marked increase in the permeability of the barrier (Swithinbank and others, 1953, Fig. 14 and Table VII).

The results obtained with sodium bromide were rather different.

Effects of the Complete Reaction

The bromide ratio has now been estimated throughout four complete reactions. These reactions were induced by injecting 3·75 μg. of the purified protein derivative of tuberculin (P.P.D.) at lumbar puncture into the C.S.F. and subsequently collecting samples of blood and lumbar C.S.F. at regular intervals (usually once daily). The findings are summarized in Table I. In every instance the bromide ratio fell to the order of unity within three days of the injection of P.P.D., and in two cases within 24 hours. In other words, the blood-C.S.F. barrier to bromide was abolished during the first, polymorphonuclear, phase of the reaction.

During the second, lymphocytic, phase the bromide ratio either remained low or showed a further fall to values well below unity. As the second phase of the reaction subsided, so the bromide ratio began to climb, but was still well below the limits of normal during the third week of the reaction. In one case (E. M.) observations were continued at frequent intervals for many weeks, and it was not until the eighty-eighth day after the injection of P.P.D. that the bromide ratio reached the lower limit of normal (Table I).

The typical behaviour of the bromide ratio in relation to the disturbances in cell and protein contents of the C.S.F. is shown in Fig. 1 (Case E. M.). In this case penicillin was also used as an indicator. Whereas most penicillin appears in the C.S.F. at the peak of the second phase, the maximal rate of fall in the bromide ratio coincides with the onset of the first wave of pleocytosis and rise in protein content. There is, however, no indication of a rise in the bromide ratio corresponding with the rapid

TABLE I

BROMIDE RATIOS IN FOUR COMPLETE INTRATHECAL TUBERCULIN REACTIONS IN SUBJECTS WITH NORMAL MENINGES

Case	Bromide Ratio when P.P.D. Given	Lowest Value during 1st Phase	Days after Injection	Lowest Value during 2nd Phase	Days after Injection	Value during 3rd Week	First Value in Normal Range	Day of Occurrence
E.M.	2·65	0·99	2nd	0·85	8th	1·05	2·17	88
W.S. (i)	2·48	0·95	1st	1·35	7th	1·8	Not recorded	
W.S. (ii)	2·75	1·09	1st	0·77	6th	1·89	Not recorded	
P.P.	2·81	1·01	3rd	1·02	5th	1·48	Not recorded	

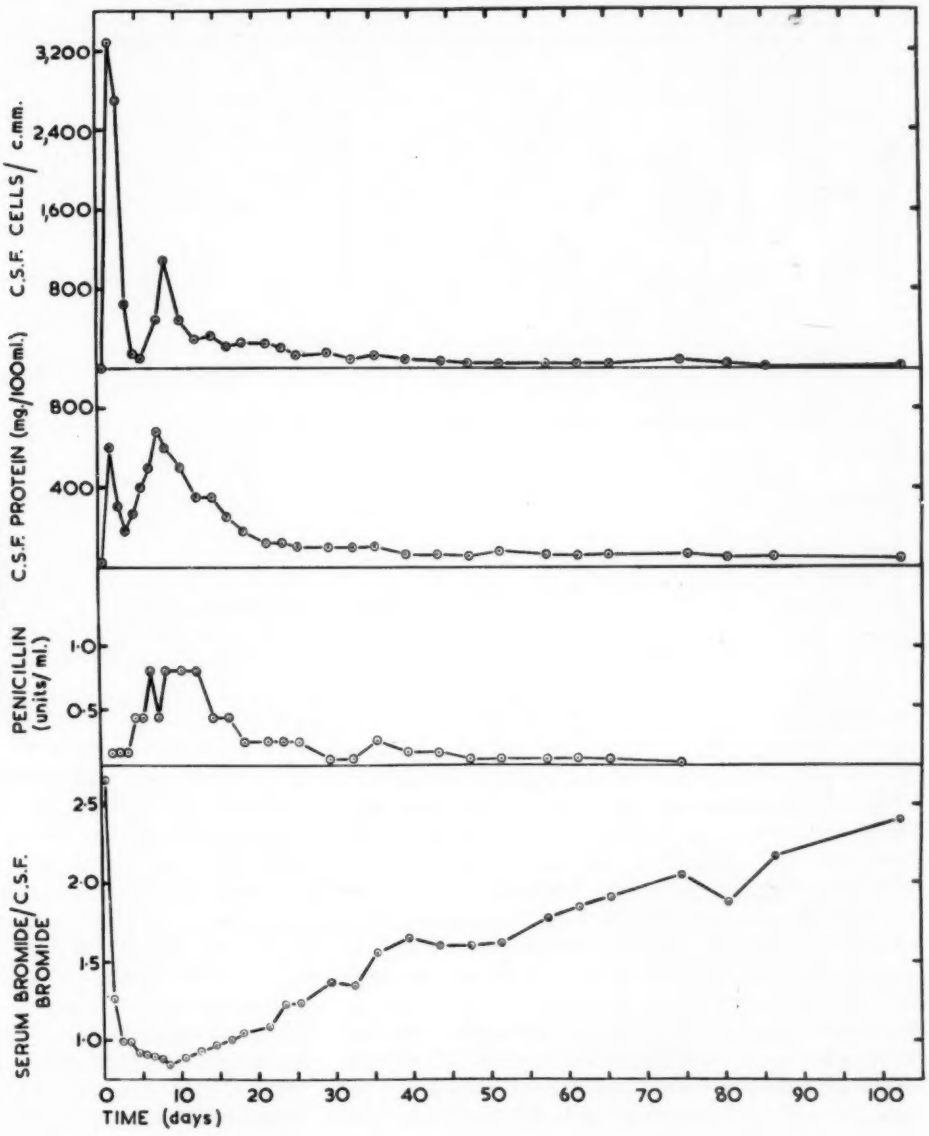

FIG. 1.—Effect of intrathecal P.P.D. on C.S.F. cells and protein, and on the penetration of penicillin and bromide from blood to C.S.F. in subject with normal meninges (Case E. M.). 3·75 μg P.P.D. by lumbar injection on Day 1. Last dose of oral sodium bromide 72 hours before Day 1.

fall in cell count and protein content that marks the end of the first phase of the reaction. The second phase of the reaction is accompanied by a further small fall in the bromide ratio. As this second phase subsides, the bromide ratio slowly begins to climb, but its return to within normal limits is delayed well beyond that of the protein content.

The dissociation that appears as the reaction evolves between the increase in the permeability of the barrier to bromide and the intensity of the meningeal inflammation is further illustrated by Table II. This shows the daily values obtained for the bromide ratio compared with the total cell counts and protein estimations during the first phase of the reaction in Case P. P. During the first 24 hours

TABLE II

TOTAL CELL COUNT AND PROTEIN CONTENT OF THE C.S.F., TOGETHER WITH THE BROMIDE RATIOS THROUGHOUT THE FIRST FIVE DAYS OF A COMPLETE INTRATHECAL TUBERCULIN REACTION

	Time in Days				
	1	2	3	4	5
Bromide ratio	2·81	1·33	1·19	1·01	0·99
Cells/c.mm.	12	4,560	2,510	350	254
Protein (mg./100 ml.)	30	300	170	160	180

P.P.D. given on Day 1.

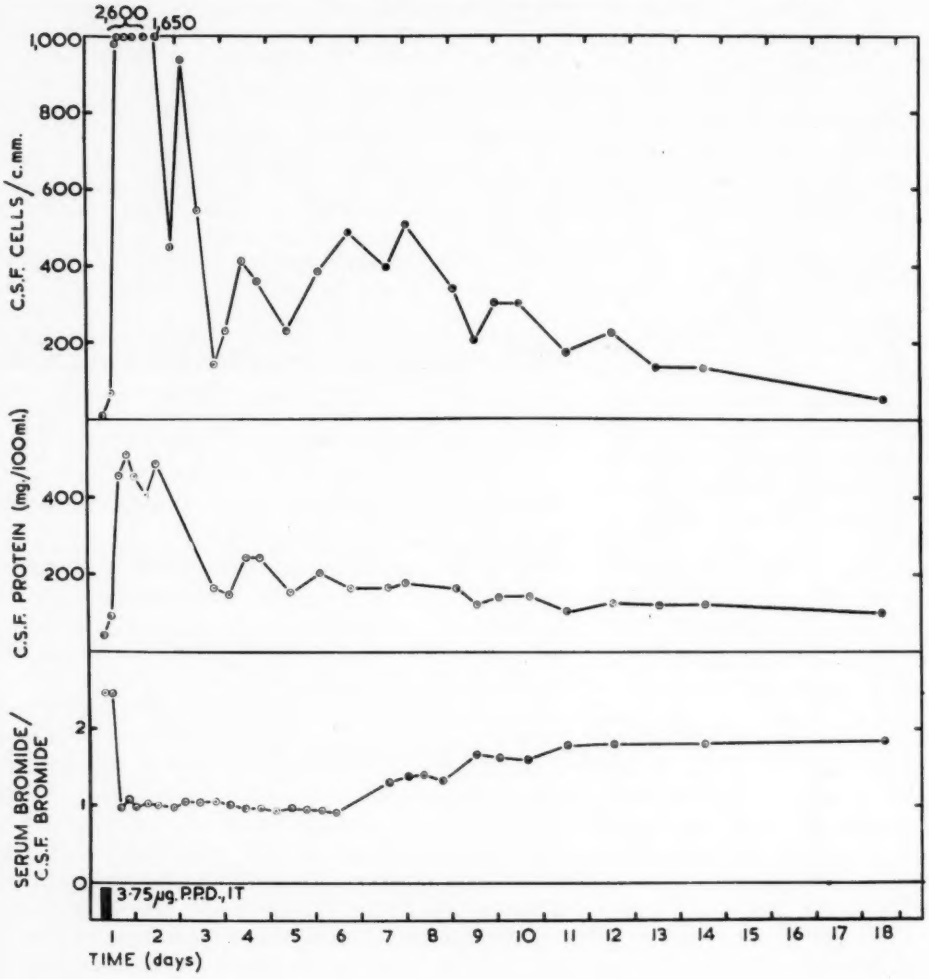

FIG. 2.—Effect of intrathecal P.P.D. on C.S.F. cells and protein and on the bromide ratio in subject with normal meninges (Case W. S.).

The lumbar C.S.F. was examined every four hours during the first five days of the reaction.

Last dose of oral sodium bromide 57 hours before Day 1. 3·75 µg P.P.D. by lumbar injection at first tap on Day 1.

the bromide ratio falls as the meningeal reaction develops, but thereafter the ratio continues to fall, even though the inflammation, as judged by the cell counts and protein estimations, is steadily waning.

In one case the early stages of the reaction were studied in more detail by means of lumbar puncture done every four hours (Swithinbank and others, 1953, Fig. 3). Fig. 2 shows the astonishing rapidity with which the barrier was abolished. Four hours after the injection the bromide ratio had not altered significantly, but by the eighth hour it had fallen to unity.

Effect of the Incomplete Reaction

When the tuberculin sensitivity of the recipient is low, or is artificially induced by vaccination, the intrathecal reaction is usually incomplete, the commonest anomaly being absence of the second, or lymphocytic, phase (Swithinbank and others, 1953, Table V and Fig. 11). The bromide ratio has now been followed throughout four such abortive reactions (Table III). As in the complete reaction, the bromide ratio fell steeply during the first 24 hours, though it never reached unity. This depression was, however, quite short lived, and by the end of the second week the barrier was fairly well re-established.

Effect of Benadryl

As there is some evidence suggesting that antihistaminic drugs can modify both the intradermal (Sarber, 1948 ; Graub and Barrist, 1950) and intrathecal tuberculin reaction (Swithinbank and others, 1953), the following observations were made.

The subject, P. P., who had already shown a complete intrathecal reaction accompanied by typical changes in the blood-C.S.F. barrier to both bromide and penicillin (see Tables I and II), received a second lumbar injection of P.P.D. some months later. On this second occasion, however, 75 mg.

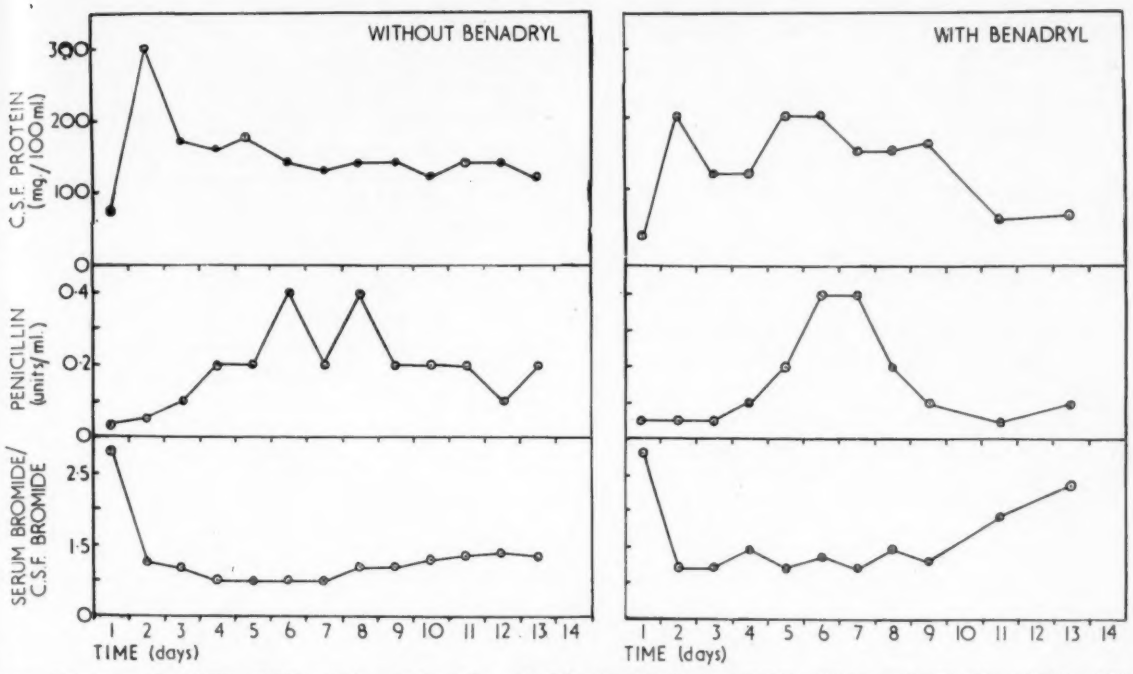

FIG. 3.—Behaviour of penicillin, C.S.F. protein, and bromide ratio following intralumbar P.P.D. without and with "benadryl"; 3·75 μg P.P.D. by lumbar injection on Day 1 in both régimes. Benadryl, 75 mg., given by mouth every four hours throughout second reaction.

"benadryl" was given by mouth every four hours throughout the period of observation and the injection of P.P.D. given only after the first three doses.

When no "benadryl" was given the cell count 24 hours after the injection of P.P.D. was 4,560 per c.mm., with 94% polymorphonuclears, and there was a well marked second rise in the cell count which reached a maximum on the sixth day. In the second reaction, however, the total cell count 24 hours after injection was only 900 per c.mm. (80% polymorphonuclears), while there was no significant second rise.

The protein and penicillin contents of the C.S.F. throughout both reactions are shown in Figs. 3a and 3b, together with the bromide ratios. When "benadryl" was given the rise in protein content was both smaller and less persistent than in the first reaction. The initial fall in the bromide ratio was identical in the two reactions; but whereas, when no "benadryl" was given, the fall continued for another two days and the rise was so delayed that on the thirteenth day the ratio was still only 1·34, in the second reaction there was no further fall after the first day and by the thirteenth day the ratio had risen to 2·1, i.e., to within the lower limit of the normal range. Similarly with the penicillin: its passage from blood to C.S.F. was facilitated in both reactions but the return to normal was accelerated when "benadryl" was given. It appears, therefore, that in this case at least the administration

TABLE III

BROMIDE RATIOS IN FOUR INCOMPLETE INTRATHECAL TUBERCULIN REACTIONS

Case	Bromide Ratio when P.P.D. Given	Lowest Value during 1st Phase	Days after Injection	Lowest Value during 2nd Phase	Days after Injection	First Normal Value	Day of Occurrence	Remarks
C.F.	3·39	1·32	1st	1·52	5th	2·2	10th	Low sensitization
A.W.	2·66	1·5	1st	No second phase		2·21	15th	Low sensitization
J.D.	Samples lost	1·18	1st	1·5	5th	2·34	13th	Artificial sensitization
M.W.	2·22	1·23	1st	No second phase		2·30	14th	Artificial sensitization

of "benadryl" hastened the restoration of the blood-C.S.F. barrier to protein, bromide, and penicillin.

Effect of Cortisone

It has been amply shown that cortisone and A.C.T.H. can modify tuberculin sensitivity as judged by their effect on the intradermal tuberculin reaction (Long and Favour, 1950). Their mode of action is obscure (Long, Miles and Perry, 1951), but that cortisone, at least, is active on local as well as on systemic administration has been demonstrated both in the skin (personal observation) and in the anterior chamber of the eye. As there is also evidence that A.C.T.H. is able to bring about a rapid decrease in the abnormalities of the C.S.F. seen in tuberculous meningitis (Bulkeley, 1953), it seemed desirable to study the effect of cortisone on the intrathecal tuberculin reaction. The following two experiments were therefore performed.

Two subjects (A. G. and W. S.), in whom the Mantoux test was strongly positive to O.T. 1/1,000 and each of whom had previously shown a complete intrathecal tuberculin reaction to 3·75 μg P.P.D., received an intravenous injection of sodium bromide. Forty-eight hours later both received an intrathecal injection of 3·75 μg P.P.D. by lumbar puncture. At the same time one (W. S.) was given 50 mg. cortisone by mouth, and the other (A. G.) 5 mg. cortisone intrathecally. The subsequent reactions and their effect on the blood-C.S.F. barrier to bromide and, in Case W. S., to penicillin, were followed in the usual way. The results are shown in Table IV.

When 50 mg. cortisone was given by mouth there was an almost complete suppression of the polymorphonuclear component of the reaction: the total cell count 24 hours after injection was 540 per c.mm., but only 4·4% of these were polymorphonuclears. The protein component, the second phase of the reaction, and the facilitation of the passage of penicillin were not significantly altered. In spite of the considerable modification of the first phase, the bromide ratio still fell sharply during the first 24 hours of the reaction, though the level it reached, i.e., 1·24, was well short of unity. By the next day the ratio had already risen appreciably, and by the eleventh day was within normal limits. A similar though less well marked effect was seen when 5 mg. cortisone was given by intrathecal injection.

From these very limited observations it appears that both "benadryl" and, to a greater extent, cortisone are capable of modifying the intrathecal tuberculin reaction, the one by damping down the second phase and the other the first phase of the reaction. Both these anomalies can occur naturally, either when a very small dose of P.P.D. is given or when the sensitivity of the recipient is low (Swithinbank and others, 1953, Figs. 1 (a) and 11). It is of interest that both when the reaction was naturally anomalous and when it was artificially modified the return of the bromide ratio to normal was accelerated. It appears, therefore, that cortisone and, to a lesser extent, "benadryl" are antagonistic to tuberculin in their effect on the blood-C.S.F. barrier.

Effect of Intramuscular Tuberculin

It has already been shown that the intramuscular injection of tuberculin has no effect either on the

TABLE IV

EFFECT OF CORTISONE ON THE BEHAVIOUR OF THE CELL AND PROTEIN CONTENTS OF THE C.S.F. AND THE BROMIDE RATIOS THROUGHOUT THE INTRATHECAL TUBERCULIN REACTION

Days	1	2	3	4	5	6	7	8	9	10	11	14–16
CASE W.S. *Reaction I*												
Cells/c.mm.	14	2920	538	410	236	483	393	507	205	300	300	134
% Polymorphs	0	90	31	5	14	1	0·5	0·5	0	0·5	0·5	1
Protein (mg./100 ml.)	40	400	160	240	148	160	160	180	120	140	100	120
Bromide ratio	2·48	1·04	1·06	0·96	0·96	0·91	1·31	1·36	1·65	1·63	0·79	1·8
Reaction II (bovine P.P.D.)												
Cells/c.mm.	1	2450	—	720	—	536	—	1728	—	1000	—	378
% Polymorphs	0	70	—	?	—	0·05	—	0·05	—	0·05	—	3
Protein (mg./100 ml.)	30	360	—	360	—	360	—	240	—	200	—	180
Bromide ratio	2·75	1·09	—	0·93	—	0·77	—	0·83	—	0·87	—	1·24
Reaction III (cortisone 50 mg. p.o.)												
Cells/c.mm.	3	540	310	450	542	500	390	536	332	—	159	170
% Polymorphs	0	4·4	6	2	0	0	0	1	1	—	0	0
Penicillin	0	<0·05	0·05	?	0·1	0·05	0·1	>0·05	0·05	—	0·05	—
Protein (mg./100 ml.)	40	300	120	180	180	160	120	140	140	—	100	60
Bromide ratio	3·44	1·24	1·46	1·32	1·42	1·19	1·71	1·39	1·61	—	2·5	2·7
CASE A.G. (cortisone 50 mg. I.T.)												
Cells/c.mm.	0	252	154	228	148	208	233	264	270	—	163	139
% Polymorphs	0	47	16	10	1·5	0	0·5	1·6	2·5	—	0	0
Penicillin	0	<0·05	0·05	<0·05	0·1	0·05	0·1	0·05	—	—	—	—
Protein (mg./100 ml.)	35	120	120	120	120	100	120	120	120	—	110	60
Bromide ratio	2·75	1·41	1·41	1·4	1·31	1·5	1·54	1·54	1·49	—	1·74	2·03

P.P.D. given on Day I.

TABLE V

DISTRIBUTION OF THE BROMIDE RATIOS AT THE OUTSET OF TREATMENT IN 45 CASES OF TUBERCULOUS MENINGITIS TOGETHER WITH THE STAGE OF THE DISEASE AND ULTIMATE OUTCOME

Bromide Ratio		<0·7	0·7–0·99	1·0–1·29	1·3–1·59	1·6–1·89	2·0–2·19	>2·19	Total
No. of Cases		0	18	19	5	2	1	0	45
Cases : Stage of Disease	"Early"	—	4	4	1	1	1	—	11
	"Intermediate"	—	12	12	3	—	—	—	27
	"Late"	—	2	3	1	1	—	—	7
Died		—	5	4	1	0	0	—	10

cell and protein contents of the C.S.F. or on the blood-C.S.F. barrier to penicillin (Swithinbank and others, 1953, Fig. 13). The bromide ratio has also been estimated daily for six days following the intramuscular administration of tuberculin in a dose sufficient to cause a clinical reaction. No significant change in the ratio was seen.

The Bromide Ratio in Tuberculous Meningitis

The effect of tuberculous meningitis on the blood-C.S.F. barrier to bromide is identical with that of the experimental intrathecal tuberculin reaction. During the active stage of the disease a profound fall in the bromide ratio is the rule, with a return towards normal as convalescence advances. This depression of the bromide ratio has proved so characteristic of tuberculous meningitis, as opposed to other varieties of "lymphocytic" meningitis with comparable changes in the C.S.F., that it has provided the basis for a diagnostic test (Taylor and others, 1954).

The bromide ratio has now been estimated in 45 cases of tuberculous meningitis during the first month, and usually during the first week, of admission to hospital. The diagnosis was confirmed bacteriologically in every case but one; no patient had received any tuberculin at the time of the tests, and none showed any evidence of spinal block. The results are shown in Table V. Of the 45 cases, in 37 the ratio was less than 1·3 and in 18 it was less than unity, while in only three did it exceed 1·6.

Table V shows the distribution of these cases in regard both to the stage of the disease at the outset of treatment and to the ultimate mortality. The stage of the disease is defined as "early", "intermediate", and "late" in terms of a simple classification based, not on duration of symptoms, but on the patient's clinical condition (Medical Research Council, 1948), and it is now established that, given adequate treatment, it is the stage reached by the disease when treatment is begun that is the overriding factor in prognosis (Lorber, 1954). In this series of cases the time when treatment was begun corresponds with fair accuracy to the time the bromide test was performed.

It is clear from Table V that the characteristic and profound depression of the bromide ratio is independent of the stage of the disease and therefore of the ultimate prognosis. For example, of the 11 cases in which the disease was still at the "early" stage, in eight the bromide ratio was already lower than 1·3 and in four it was below unity. At the other end of the scale, of those three exceptional cases in which the bromide ratio exceeded 1·6 the disease was in the "early" stage in two, but in the third was very advanced.

It appears, therefore, that the depression of the blood-C.S.F. barrier is something more than an expression of the extent and intensity of the inflammatory changes in the leptomeninges. This conclusion is supported by the finding that, in tuberculous meningitis, there is no quantitative relationship between the depression of the bromide ratio and either the cell count or protein content of the C.S.F. Thus, while it is true that a high protein content of, for example, 400 mg. per 100 ml. or over, has always been accompanied by a low bromide ratio, the converse does not hold, and ratios of unity or below have not infrequently been found in fluids that contained less than 100 mg. protein per 100 ml. (Taylor and others, 1954, Fig. 3).

As the active meningeal infection is controlled, so the blood-C.S.F. barrier to bromide is gradually restored. Table VI shows the distribution of cases according to the ratios found during the period of intrathecal medication*, which corresponds with the period of active infection as judged by certain well defined clinical and pathological criteria (Cairns and Smith, 1952; Smith, 1952), compared with the ratios found at the first estimation and during convalescence. As already stated, all the first estimations were done during the first month in hospital, and the great majority during the first week. The estimations tabulated as "during treatment" were done later than the first month, and where several had been done the earliest was chosen. When P.P.D. was used in treatment the values obtained just before the injection were

* It has already been shown that intrathecal medication alone, in the absence of active tuberculous meningitis, has no significant effect on the blood-C.S.F. barrier to bromide (Taylor and others, 1954).

TABLE VI
DISTRIBUTION OF THE BROMIDE RATIOS THROUGHOUT THE COURSE OF THE ILLNESS IN TUBERCULOUS MENINGITIS

	No. of Cases	<0·7	0·7–0·99	1·0–1·29	1·3–1·59	1·6–1·89	1·9–2·19	>2·19	Mean
1st Estimation	45	0	18	19	5	2	1	0	1·13
During I.T. treatment without P.P.D.	14	0	5	4	3	0	2	0	1·2
During I.T. treatment with P.P.D.	22	1	9	6	6	0	0	0	1·07
Early convalescence	29	0	0	3	11	7	5	3	1·71
Late convalescence	22	0	0	0	3	6	6	7	2·02

chosen rather than those at the height of the reaction. "Early convalescence" is defined as any time between the conclusion of the intrathecal medication and the end of the sixth month in hospital, and "late convalescence" as between the conclusion of intrathecal medication and the end of the first year. Where several such estimations were done the latest were chosen.

Table VI shows that, whether or not P.P.D. is used in treatment, the peak incidence during the stage of active infection remains the same as at the time of the first estimation and lies between 0·7 and 1·29. During early convalescence the peak shifts to the right, to lie between 1·3 and 1·89. This shift becomes still more marked during late convalescence, when the mean value for a total of 22 cases is 2·02, that is to say, at the lower limit of normal (Fig. 4).

The behaviour of the blood-C.S.F. barrier to bromide throughout the course of the illness is exemplified by the following case, in which serial estimations of the bromide ratio were done for both lumbar and cisternal fluid and in which intrathecal P.P.D. was not used in treatment.

Case No. 182.—A regular soldier aged 26 years was admitted to the Military Hospital for Head Injuries, Wheatley, on March 3, 1953, suffering from Pott's disease with incipient paraplegia, chronic phthisis, and renal tuberculosis. During the first three weeks in hospital he developed obvious signs of meningitis, and lumbar puncture on March 24 yielded a fluid which showed the characteristic changes of tuberculous meningitis and in which *M. tuberculosis* was identified by direct examination and culture. Treatment was begun immediately with daily intrathecal and systemic administration of both streptomycin and isonicotinic acid hydrazide (I.N.A.H.). Because of the extent and severity of the systemic disease, tuberculin was given by intramuscular injection, but no intrathecal P.P.D. was injected for fear of exacerbating the paraparesis.

The daily intrathecal medication was continued for a total of 190 days and the intramuscular streptomycin for 200 days. The streptomycin was then stopped because of incipient deafness, but the oral I.N.A.H. and *para*-amino-salicylic acid (P.A.S.) were continued for a total of 400 days.

For the first month the patient remained critically ill. He then slowly but steadily improved, and 15 months after the beginning of treatment he was free from all signs and symptoms and on full activity, though still wearing a spinal brace. Radiographs of the chest and spine showed satisfactory healing, and the urine was normal in all respects. The C.S.F. then contained 70 mg. protein per 100 ml. as its only abnormality, while repeated cultures of C.S.F., urine, and laryngeal swabs had all been negative for many months.

Serial estimations of the bromide ratio were made

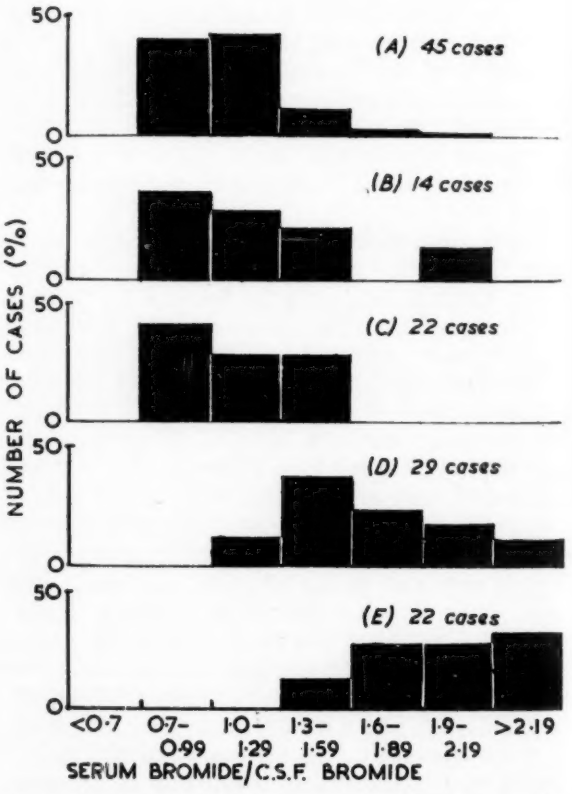

FIG. 4.—Bromide ratios during the course of the illness in tuberculous meningitis. A, at outset of treatment. B, during period of intrathecal medication. No P.P.D. given. C, during period of intrathecal medication. P.P.D. used in treatment. D, during early convalescence. E, during late convalescence.

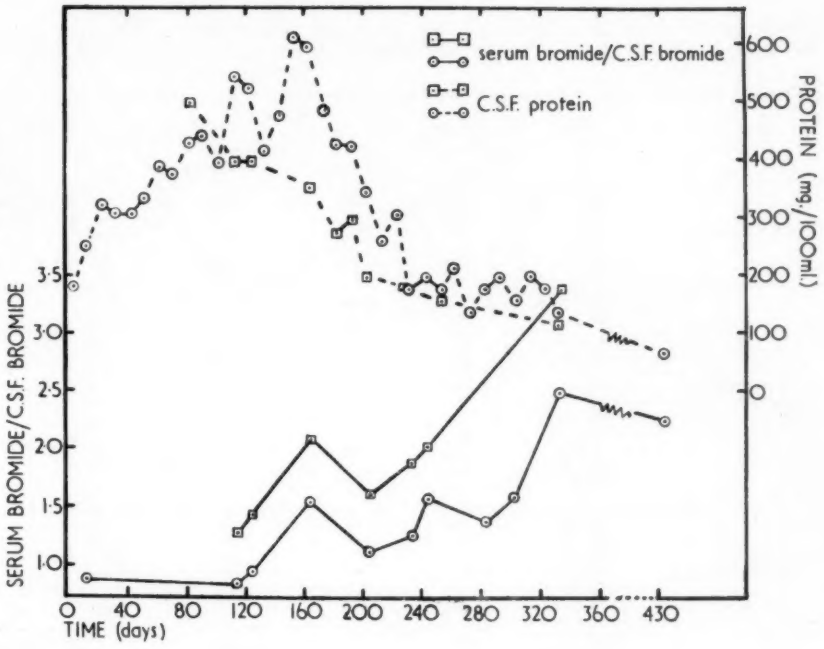

FIG. 5.—Protein content (mean for each 10-day period) and bromide ratio for both cisternal and lumbar C.S.F. throughout the course of the illness in Case 182. No intrathecal P.P.D. given. Meningeal infection considered obsolete after 190 days.

throughout the illness. The results are shown in Fig. 5, together with the average value of the protein content of the lumbar C.S.F. for each 10-day period of treatment.

It has been found that the behaviour of the protein content of the C.S.F. reflects the activity of the meningeal infection fairly accurately (Cairns and Smith, 1952). In this case repeated cisternal punctures were done in order to make sure that the high protein levels in the lumbar C.S.F. were not due simply to the local effect of the spinal lesion. As the protein values for lumbar C.S.F. were closely paralleled by those for cisternal, they were in all probability an accurate index of the progress of the meningitis. When the infection was obsolescent, as indicated by a sustained fall in the protein curve, so the bromide ratio for lumbar fluid steadily rose and was paralleled by a rise in the ratio for cisternal fluid, though at a higher level.

Other evidence that a return of the bromide ratio to within the limits of normal is an indication that the meningeal infection is obsolete was provided by three fatal cases in which the patients died from causes other than the meningitis. Estimation of the bromide ratios during late convalescence gave values of 2·0, 2·25, and 2·48 respectively, and careful post-mortem studies confirmed that in all three cases the meningitis was well healed. By contrast, in a fourth case in which the patient died from a recrudescence of the meningitis after withdrawal of the intrathecal medication, the bromide ratio at the end of the previous course of treatment never rose above 1·08.

A bromide ratio of 2·0 or higher has now been found in 25 cases at a time when, on clinical grounds, the infection was thought to be obsolete. None of these patients has yet shown any evidence of relapse, but the follow-up period is still too short for the restoration of the blood-C.S.F. barrier to bromide to be accepted as a criterion of cure.

The Bromide Ratio at Different Levels of the Neuraxis

It has already been shown that, in the absence of meningitis, fluid withdrawn from the lateral ventricles contains only about one half the amount of bromide of the lumbar C.S.F. The bromide ratio (S/V) is correspondingly higher and normal values probably range between 3·28 and 4·9. Such few observations as have been made on fluid withdrawn from the cisterna magna indicate that the ratio serum bromide/cisternal C.S.F. bromide (S/C) lies between that for lumbar (S/L) and for ventricular (S/V) C.S.F. (Hunter and others, 1954).

The bromide ratio for either ventricular or for cisternal fluids, or for both, has now been estimated simultaneously with that for lumbar C.S.F. in several cases of tuberculous meningitis and also at different stages of the illness in the same case. The results are shown in Table VII, together with the protein content of the C.S.F. The bromide ratio for ventricular fluid (S/V) has invariably been higher than that for lumbar (S/L), while the cisternal ratio

TABLE VII

SIMULTANEOUS ESTIMATIONS OF THE BROMIDE RATIO FOR LUMBAR C.S.F. AND FOR EITHER CISTERNAL OR VENTRICULAR FLUID OR BOTH AT DIFFERENT PERIODS IN THE ILLNESS AND WITH AND WITHOUT MANOMETRIC SPINAL BLOCK

Stage of Illness	Serial No.	Spinal Block	Lumbar (L)		Cisternal (C)		Ventricular (V)	
			S/L	Protein (mg./100 ml.)	S/C	Protein (mg./100 ml.)	S/V	Protein (mg./100 ml.)
On admission	166	No	1·07	210	Not recorded		1·38	10
	173	No	0·93	150	Not recorded		2·27	45
	202	No	1·29	160	2·94	68	Not recorded	
	54X	No	1·08	174	—	—	1·9	85
	207	Yes	0·79	750	—	—	2·78	27
During intrathecal treatment	140	No	0·89	295	1·26	76	Not recorded	
	145	No	1·05	125	2·42	40	Not recorded	
	154	No	0·97	143	—	—	3·04	7
	182 (i)	No	0·88	520	1·31	325	—	—
	20X	No	0·94	—	1·05	—	1·39	—
	46X	No	1·12	105	Not recorded		3·08	35
	112	Yes	0·96	—	1·49	—	1·58	—
	125 (i)	Yes	1·01	4400	1·48	87	—	—
	23X	Yes	0·89	1332	Not recorded		2·14	23
	52X	Yes	0·87	1600	1·98	32	3·10	20
	39X (i)	Yes	0·87	530	1·28	100	Not recorded	
	55X	Yes	0·81	95	1·74	15	Not recorded	
Early convalescence	106 (i)	No	1·02	51	1·65	9	1·99	7
	182 (ii)	No	1·14	260	1·62	160	Not recorded	
	193 (i)	No	1·0	275	1·52	110	Not recorded	
	193 (ii)	No	1·14	190	1·55	102	Not recorded	
	125 (ii)	Yes	1·06	3950	2·57	56	Not recorded	
	39X	Yes	1·67	365	2·65	16	Not recorded	
Mid-convalescence	106 (ii)	No	2·0	45	Not recorded		3·28	23
	163	No	1·35	60	Not recorded		2·85	38
	182 (iii)	No	1·60	174	2·04	102	Not recorded	
	193 (iii)	No	1·30	173	1·79	123	Not recorded	
	19X	No	1·51	—	2·43	—	3·37	—
	125 (iii)	Yes	1·29	1200	3·45	20	Not recorded	

(S/C) has been intermediate between the two. But although the relationship S/V > S/C > S/L has so far proved invariable, it is clear from Table VII that all three ratios are depressed during the active stage of the illness and rise as convalescence advances. The characteristic relationship between S/L and S/C, and the behaviour of both during the course of the illness, are well shown by Case 182 (Fig. 6).

The gradient for the bromide content of the C.S.F. at different levels of the neuraxis is thus in the same direction as for the protein content. But whereas the disparity between the protein contents of lumbar C.S.F. and of either cisternal or ventricular fluid is greatly enhanced by the presence of manometric spinal block, the relationship between the S/L and either S/C or S/V does not appear to be proportionately affected. Nor, although the bromide and protein contents vary in the same direction, is there any quantitative relationship between them. For example, in Case 106 (i) the ratios S/C and S/V are depressed, although the protein contents are normal. Again, in Case 140, the ratio S/C = 1·26, that is to say it was greatly depressed even though the protein content was only 76 mg. per 100 ml. By comparison, in Case 182 (i) S/C = 1·31 ; that is to say it was actually a little higher than in Case 140, even though the protein content was as high as 325 mg. per 100 ml.

The Effect of the Intrathecal Tuberculin Reaction in Cases of Tuberculous Meningitis

When intrathecal P.P.D. is used in the treatment of tuberculous meningitis its effect on the bromide ratio for lumbar fluid may not be apparent because the ratio S/L is already depressed by the meningitis. Even so, the lowest values yet recorded for S/L have been found in cases of tuberculous meningitis under treatment with P.P.D., when S/L has on occasions been as low as 0·71, 0·72, and 0·68.

When treatment with P.P.D. is continued into convalescence each reaction will cause a new, though temporary depression of the ratio, just as it brings about a recurrence of the physical and mental signs of the meningitis (Williams and Smith, 1954). For this reason a low bromide ratio cannot be interpreted as evidence of continued infection until at least two weeks and probably longer have elapsed since the last intrathecal injection of P.P.D.

The effect of the intrathecal tuberculin reaction is seen better in cisternal than in lumbar fluid because the ratio S/C is usually well above unity even at the height of the infection. When, however, P.P.D. is injected directly into the cisterna

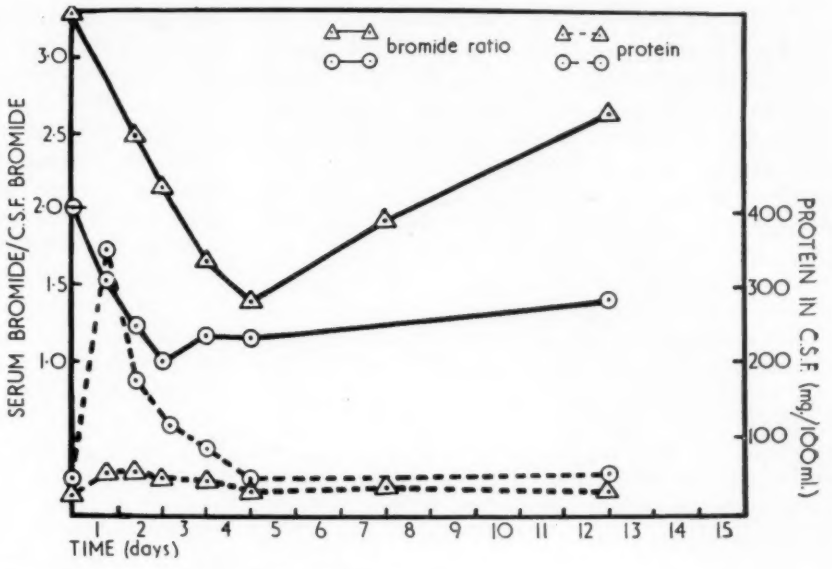

FIG. 6a.—Behaviour of bromide ratio and lumbar and ventricular C.S.F. protein following lumbar injection of 7·5 μg P.P.D. on Day 1. Last oral dose of sodium bromide six days before Day 0.

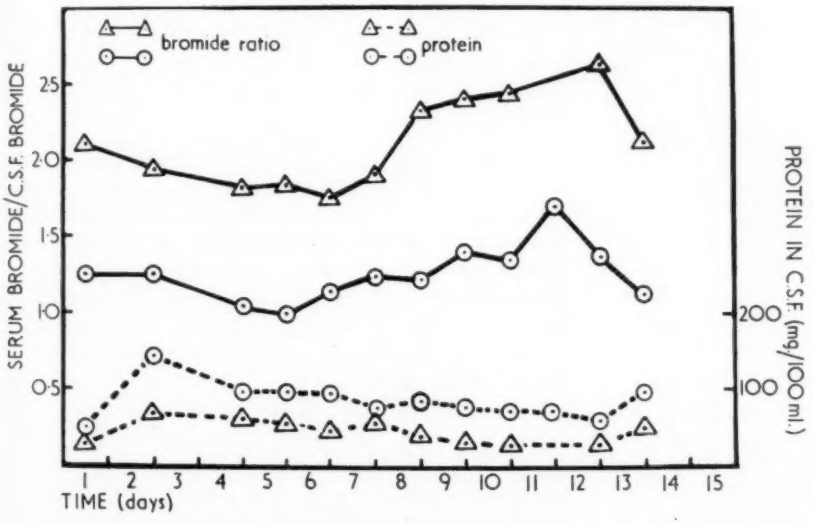

FIG. 6b.—Behaviour of bromide ratio and lumbar and ventricular C.S.F. protein following intraventricular injection of 7·5 μg P.P.D. on Day 1. Last oral sodium bromide 48 hours before Day 1.

magna the ratio S/C falls towards unity as the reaction develops and then re-establishes itself as the reaction subsides.

The effect of the reaction on the ratio for ventricular fluid was studied in Case 106, in which two reactions were provoked during late convalescence. In the first the P.P.D. was injected by lumbar puncture and in the second by ventricular puncture. The behaviour of the protein contents and of the ratios S/L and S/V throughout both reactions is shown in Figs. 6a and 6b. When the P.P.D. was given by lumbar puncture there was a brisk rise in the protein content of lumbar C.S.F., accompanied by the expected fall in S/L. The protein content of the ventricular fluid was, however, little disturbed, and although the ratio S/V was depressed the fall was not only delayed well beyond that of S/L (Fig. 6a) but was never so marked. This relationship was preserved even when the P.P.D. was injected directly into the ventricle. The resulting rise in protein, though small, was greater in the lumbar than in the ventricular fluid, while the fall in S/V was not only considerably smaller than that of S/L but did not reach its maximum until S/L had begun to increase (Fig. 6b).

It appears, therefore, that while the effect of the intrathecal tuberculin reaction on the blood-C.S.F. barrier to bromide is similar for both lumbar and cisternal fluid, it is different for ventricular fluid in that the rise in the bromide content of the ventricular fluid is both smaller and slower than in lumbar C.S.F.

Discussion and Conclusions

Many attempts have been made in the past to increase the permeability of the blood-C.S.F. barrier and so render the central nervous system more accessible to therapy. For example, there is a considerable body of literature on the use of theophylline, urotropine, salicylates, and other substances as adjuvants to arsenic, quinine, and therapeutic sera. Most of such work, however, is either frankly disappointing or lacks quantitative criteria and is therefore inconclusive. Nor is it easy to find definite evidence of any agent that changes barrier permeability from among the extensive observations that have been made with dyes. There are, of course, a great many accounts of the increase in permeability of the barrier in certain diseases, and particularly in meningitis ; but once again quantitative data are largely wanting, hence the diversity of opinion that persists as to the efficacy or otherwise of systemic chemotherapy in the treatment of meningitis.

Perhaps the first really promising approach towards a quantitative method for assessing changes in the blood-C.S.F. barrier was made when Walter described his bromide distribution test (Walter, 1929). The full value of this test has, however, only become apparent since precise methods for bromide determination have been developed (Hunter, 1953 ; Hunter and Goldspink, 1954). The bromide test possesses certain unique advantages and should provide a useful method for assessing the efficacy of agents that are claimed to alter the permeability of the barrier. The test has proved useful in both the diagnosis and management of tuberculous meningitis, but what is more important is that it has made it possible to demonstrate the profound and dramatic effect on the blood-C.S.F. barrier exerted by tuberculin when this is introduced into the C.S.F. of the sensitized subject. We can find no record of a comparable effect produced by any specific factor ; still less by a factor that occurs in nature and in amounts that are probably of the same order as those used experimentally.

The results of the bromide test in tuberculous meningitis, in other varieties of " lymphocytic " meningitis, and in the intrathecal tuberculin reaction, together with observations made on the passage of penicillin from blood to C.S.F., go some way towards resolving the confusion that exists concerning the effect of leptomeningitis on the permeability of the blood-C.S.F. barrier. In the first place, study of the intrathecal tuberculin reaction shows that the effect of a given inflammatory process on the blood-C.S.F. barrier is not necessarily uniform in respect of different substances. Thus, in the complete reaction the permeability of the barrier is increased for both bromide and penicillin, though to a different degree ; but the maximal effect for the two substances is seen at different stages of the reaction. Further, in those anomalous reactions in which the second phase is lacking the passage of bromide is still greatly facilitated (Table III), although the barrier to penicillin is not detectably affected (Swithinbank and others, 1953, Table VII).

Again, the contrast between the low bromide ratio so characteristic of the intrathecal tuberculin reaction and of tuberculous meningitis, and the much higher ratios found in other varieties of " lymphocytic " meningitis shows that the effect on the barrier varies with the aetiological agent. We have not as yet had many opportunities for studying the bromide ratio in acute purulent meningitis, but such observations as have been made support this conclusion, since it is apparent that the barrier is neither so regularly nor so profoundly affected as in tuberculous meningitis. For example, in one case of pneumococcal meningitis the bromide ratio never fell below 1·84, and early in the illness, at a time when pneumococci could still be isolated from the C.S.F., it was as high as 2·16.

Since, therefore, the effect of meningeal inflammation on the blood-C.S.F. barrier varies with the aetiology of the inflammation and with respect to different substances, it follows that no valid generalization can yet be made concerning the effect of leptomeningitis on the passage of medicaments from blood to C.S.F. It follows, too, that the great increase in barrier permeability seen in the intrathecal tuberculin reaction and in tuberculous meningitis must depend on something other than straightforward, non-specific meningeal inflammation. This conclusion is supported by the detailed observations made during the experimental reaction. Judging by the height of the pleocytosis and protein content of the C.S.F., the intensity of the inflammation is greatest during the first, or polymorphonuclear, phase. Yet the greatest penetration of penicillin and the maximal depression of the bromide ratio, though not its rate of fall, coincided with the second, or lymphocytic, phase of the reaction. Moreover, during the interval between the two phases facilitation of the passage of both bromide and penicillin may still increase, even though the pleocytosis and elevation in protein content are subsiding rapidly (Fig. 1 and Table II).

It has already been shown that the meningeal disturbances that follow the introduction of tuberculin into the C.S.F. of a sensitized subject is the direct result of an antibody-antigen reaction (Swithinbank and others, 1953). There is, moreover,

good reason to believe that the C.S.F. changes of tuberculous meningitis are also the expression of similar, though spontaneous, intrathecal tuberculin reactions (Taylor, Smith, and Vollum, 1955). It is suggested, therefore, that the marked depression of the barrier is in some way a function of the hypersensitive response as such; and that in those varieties of meningitis in which the barrier is little affected some mechanism other than an antibody-antigen reaction is responsible for the inflammation.

The choroid plexus is commonly credited with playing a predominant, if not exclusive, part in elaboration of the C.S.F. This is not the place to discuss the vexed question of where the so-called blood-C.S.F. barrier is situated nor to speculate on its nature. It should, however, be noted that the bromide test promises to provide a useful tool not only for studying the effect produced on the barrier by different pathological processes but also for elucidating certain problems connected with the physiology of C.S.F. formation. Thus, the finding that lumbar fluid has invariably contained more bromide than fluid from the lateral ventricle, and that the relationship $S/V > S/L$ cannot be reversed, even by injecting tuberculin directly into the ventricle, is hardly compatible with the view that the choroid plexus is the sole, or even the chief, route by which bromide enters the C.S.F.

Summary

The bromide test has proved a valid means of measuring the permeability of the blood-C.S.F. barrier. Results are expressed as the "bromide ratio". The test has been used extensively in cases of tuberculous meningitis and also in the experimental intrathecal tuberculin reaction.

When the experimental intrathecal tuberculin reaction is fully developed the blood-C.S.F. barrier is abolished to bromide and impaired to penicillin. In abortive reactions the barrier to bromide is still seriously impaired but is restored more rapidly than after the complete reaction.

There is no quantitative relationship between the intensity of the inflammation of the meninges, as judged by the height of the pleocytosis and protein content of the C.S.F., and the depression of the barrier.

Cortisone and, to a lesser extent, "benadryl" appear to be antagonistic to tuberculin in their effect on the blood-C.S.F. barrier.

The effect of tuberculous meningitis on the blood-C.S.F. barrier to bromide is identical with that of the experimental intrathecal tuberculin reaction. The ratio remains low as long as the infection is active and returns to normal during convalescence.

Studies of the bromide ratio for ventricular (S/V), cisternal (S/C), and lumbar C.S.F. (S/L) show that the relationship $S/V > S/C > S/L$ is invariable. In active tuberculous meningitis all three ratios are depressed but their relationship is never reversed.

The effect of the intrathecal tuberculin reaction in the presence of tuberculous meningitis is to lower all three ratios still further. The depression of S/V is delayed and smaller than that of S/L, even when the tuberculin is injected directly into the ventricle.

The significance of these findings is discussed, and it is concluded that the depression of the blood-C.S.F. barrier is a direct expression of an intrathecal antibody-antigen reaction.

It is highly unlikely that the choroid plexus is the sole, or even the chief, route by which bromide enters the C.S.F.

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THE BABINSKI RESPONSE : A REVIEW AND NEW OBSERVATIONS

BY

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REVIEW OF THE ANATOMICAL EVIDENCE

Probably the most famous sign in clinical neurology is the plantar response described by Babinski. Babinski wrote that this sign indicates a disturbance of function of the pyramidal system. Textbooks usually state, however, that this sign indicates a lesion of the pyramidal tract, and so one might well imagine that the significance of such a well established sign had been amply proved.

There are four points concerning the Babinski response that need to be stressed :

(1) Babinski stated that his sign " paraît être " ; he was not definite about the matter.

(2) Babinski eventually described two forms of abnormal plantar response. These are separate and clearly different. There is " Extension des orteils et plus particulièrement du gros orteil : j'ai appelé ce mouvement ' le phénomène des orteils ', et mes collègues ont bien voulu le dénommer ' le signe de Babinski ' (1904). There is also : " L'excitation de la plante du pied provoque parfois, entre autres mouvements réflexes, une abduction plus ou moins marquée d'un ou de plusieurs orteils " (1903). Although Babinski observed that the latter sign can be found in the normal, it is particularly common in subjects " atteints d'une perturbation du système pyramidal ". Dupré named this sign, " le signe de l'éventail ". It is usual, at least here in Britain, to speak of the Babinski response only when both these signs are present. But many workers consider the extension of the great toe as the essential sign, and speak of the Babinski response when only this sign is present.

(3) The phenomenon was described as a disturbance of functioning. Babinski at first held the opinion that there need be no anatomical or histological lesion of the pyramidal tract to account for the presence of this sign. Indeed, he recorded the presence of the sign in a case of strychnine poisoning ; when the poisoning passed off, the abnormal sign gave way to the normal response. Babinski thought that the sign could be the first and only evidence of this disturbance in functioning. Thus it did not seem to Babinski that it was necessary to give any histological verification of damage to the pyramidal tract. As he said later (1922), he was content " à se cantonner dans le domaine de l'observation clinique ".

(4) It is clear that Babinski used various methods of stimulation to obtain the response. In his original description of extension of the toes (1896), he described the stimulus as a " piqûre de la plante du pied ". In his more detailed and important communication on the new sign (1898), he wrote of the effects of stimulating the internal part and the external part of the plantar surface. And he also wrote that in some subjects it is necessary to prick the plantar surface of the foot to elicit his reflex.

Babinski's sign met with immediate success ; and as an additional sign of hemiplegia and crural monoplegia it deserved the success. This was doubtless what Babinski intended the new sign to be ; for in his time terminology was less precise than it is now. It is likely that to Babinski the terms " a sign of hemiplegia " and " a disturbance of function of the pyramidal tract " were equivalent. However, when anatomical evidence presented itself, it began to be obvious that Babinski's statements were wrong. Babinski himself reported cases which did not accord with his previous statements. For instance, in 1899, he reported three cases of paraplegia in flexion. He stated that in all three there was no histological evidence of degeneration of the pyramidal tract. Yet in the first case, the plantar responses were normal, in the second case, the " phénomène des orteils " was present, and in the third case " tickling the plantar surface of the foot gives reflex movements of the whole limb". As Babinski was concerned in this paper with demonstrating that there is such a thing as paraplegia in flexion without involvement of the cortico-spinal tracts, he seems to have failed to realize that he had recorded different forms of plantar response, one of which was the Babinski response, all present with normal cortico-spinal tracts. On his own premises, his Case 2 proved his supposition

about the significance of " le phénomène des orteils " to be wrong.

By 1911 Babinski had come to the conclusion that paraplegia in extension with increased deep reflexes is due to involvement of the cortico-spinal tracts, and that paraplegia in flexion is due to involvement of other tracts, the cortico-spinal tracts being normal or almost normal. In support of his view of the mechanism causing these two forms of paraplegia, he stated (1911) that paraplegia in extension is always accompanied by the Babinski response, whereas paraplegia in flexion is usually accompanied by this response, but can occur with a normal response. It is obvious that on his premises paraplegia in flexion should always show a normal response, for Babinski expressly stated that in this condition there is normal or almost normal functioning of the pyramidal tract. In 1912(b) he wrote that in the condition of paraplegia in extension, the " signe des orteils " is present ; and in the condition of paraplegia in flexion " dans la grande majorité des cas, le signe des orteils " is also present. Thus it will be observed that he has described the Babinski response in two conditions, in one of which the pyramidal tracts are said to be abnormal and another in which they are said to be normal.

As Babinski collected anatomical evidence, he should have been forced to the conclusion that his sign was not related to the normality or abnormality of the cortico-spinal tract. It becomes clear why he preferred to remain in a " realm of clinical observation ". He never modified his original suggestion about the significance of his sign, and never pointed out that histology failed to support the belief that the sign indicates a disturbance of the cortico-spinal tract. It is also clear from remarks that he made in discussions, reported over the years in the *Revue Neurologique*, that he forgot the evidence he had himself produced in earlier years ; he would state that with paraplegia in flexion his sign was absent, and with paraplegia in extension it was present. Finally, it is justified to point out that as neither Babinski nor any of us know what the function of the pyramidal tract is, it is impossible to discuss a perturbation of that function.

Following Babinski's original description, many papers appeared in Europe and America devoted to the new sign. As none of the authors of these papers investigated the location and extent of the lesions at post-mortem examination, these papers will not be reviewed. A glance, however, at the first paper in English describing the new sign shows how errors creep into the neurological literature. Collier (1899) examined 100 normal adults, 100 normal children, and 300 cases of nervous disease ; he had no post-mortem evidence. Nevertheless the fact that he had no evidence did not prevent him making such a statement as " According as the lesion of the pyramidal system be partial, the flexor and extensor responses may be combined in the plantar response ". Collier seems to have been the first to introduce the term flexor response for the normal response, and extensor response for the Babinski response. Collier's also seems to have been the first paper in which the common perversion of Babinski's statements is made ; for he wrote that " Babinski found " that this reflex was " pathognomonic of a lesion of the pyramidal system " ; " paraît être " has become " pathognomonic ", and " perturbation dans le fonctionnement " has become " a lesion " ; it is likely that most readers would understand under the term "a lesion ", an anatomical lesion ; indeed, this interpretation of the term was soon used by the writers of textbooks.

The literature of those cases in which histological examination of the central nervous system was carried out will now be considered in two parts. First, there will be reviewed those papers that are devoted to this sign. Secondly, cases and papers will be mentioned which have been noted during general reading of neurological literature. The authors of this material have mentioned the presence or absence of Babinski's sign *en passant* and have presented post-mortem evidence showing the location of the lesion. But these authors have not been primarily concerned with this sign ; most of them have inadvertently provided the evidence on which the relationship between the sign and the location of the lesion could be determined.

Harris (1903) devoted a paper to the Babinski response ; in his third case of hemiplegia there was a frontal glioma " pressing on the pyramidal fibres in the corona radiata " ; the contralateral plantar response had been abnormal but it was not the Babinski response.

The next authors to correlate Babinski's sign with post-mortem findings seem to have been Potts and Weisenburg (1910). They showed a case of a tumour " situated in the upper portion of the pre-central convolution " ; it primarily involved the face and upper limb, and only eventually involved the lower limb. As long as the tumour interfered with tracts supplying the face and upper limb, the plantar response was normal. As the tumour grew, " there was first present an increased patellar jerk, then hypertonicity of the whole limb with hyperextension of the great toe, and finally the Babinski response appeared". This case thus showed that the lesion has to involve that part of the tract mainly supplying the lower limb in order to get the Babinski response.

In 1912 Dejerine and Long demonstrated in Paris the histological findings in a case previously reported by Dejerine and Lévy-Valensi (1911). The patient had been an acrobat, aged 17, who had lived for 10 weeks after falling on the back of his neck ; the fall had caused a complete transverse lesion of the cord at the seventh cervical segment. During life the patient had shown absence of the deep reflexes of the lower limbs, with normal cremasteric, abdominal, and plantar reflexes. The authors were well aware of the importance of their case in providing evidence concerning the plantar responses ; the subsequent discussion reported in the *Revue Neurologique* is very important. Dejerine and Long stressed that throughout the patient's life following his fall the plantar reflexes were normal in all respects and were easily obtained. After death it was found that there was complete and total degeneration of the cortico-spinal tract, in both its lateral and ventral components. " Ce fait prouve que le signe des orteils n'est pas conditionné seulement et uniquement par la dégénérescence du faisceau pyramidal." In the ensuing discussion, Felix Rose (1912) reported a case with a complete lesion of the cord at the third thoracic segment ; in this case the cremasteric and abdominal reflexes were absent, and both plantar reflexes showed the typical Babinski response. At this meeting the important fact was pointed out by Sicard (1912) that during the course of paraplegia the reflexes often changed. Babinski (1912a) was present at the meeting, and reported in the discussion that he had seen a case in which there was an apparently complete lesion at the seventh thoracic segment, and the plantar responses were normal. Later Babinski (1912b) quoted Dejerine and Lévy-Valensi's case in support of his contention that the " réflexe de défense " may be associated with a normal plantar response or with the Babinski response ; but he did not mention that this case proved his interpretation of the relation between the cortico-spinal tract and the abnormal plantar response to be wrong.

The experience of the first world war soon showed that the Babinski response was frequently not found with proved total division of the cortico-spinal tract. The Dejerines and Mouzon (1914) reported two cases with necropsy confirmation of complete transverse lesions of the spinal cord ; neither showed the Babinski response. They emphasized that the usual reflex in such cases of total division of the cord is " la flexion plantaire du gros orteil. Le fait que dans les sections complètes de la moelle épinière la réaction à l'excitation de la plante du pied se traduit habituellement par la flexion plantaire du gros orteil, montre que, pour conditionner le signe des orteils, il faut autre chose que la dégénérescence du faisceau pyramidal ". In 1917, Guillain and Barré reported 15 similar cases, in all of which the total division of the cord was proved after death ; although the plantar responses were abnormal, they were not of the type described by Babinski.

It is sometimes stated that the removal of the function exercised by area 4 of Brodmann causes the Babinski response to appear. However, Papez and Vonderahe (1947) reported the case of a man who showed no pathological reflexes during his life. After his death it was found that area 4 was absent, and " there was a complete absence of the cortico-spinal (pyramidal) tract on the left side ".

There are two series of cases which are important although there was no necropsy evidence provided by the authors. Hyndman (1941) performed cordotomies for the relief of pain, under local anaesthetic ; from sensory testing during the operation he was able to show where in the cord he had made the incision. He was led to conclude : " In all cases of complete bilateral cordotomy, in which the anterior and anterolateral columns were sectioned, so-called signs of upper motor neuron involvement (hyperactive knee and ankle jerks, patellar and ankle clonus, and Babinski's sign) did not develop." He considered that the lateral cortico-spinal tracts would often be " partly injured, if only by transient oedema," yet " the expected signs of upper motor neuron involvement did not develop". Of great importance are those cases in which it was the purpose to divide the lateral cortico-spinal tract as therapy for severe Parkinsonism. Oliver (1953) in *Parkinson's Disease and its Surgical Treatment* reports the state of the plantar response in many such cases. The common consequence of this operation is the Babinski response, but it is far from being invariable. Oliver obtained a normal response in four cases, no response in one case, and an equivocal response in three cases ; in one case a Babinski response later became equivocal ; in one case, after dividing the lateral cortico-spinal tract on one side, he obtained a bilateral Babinski response ; and in one case, after dividing the right cortico-spinal tract in the cord, he obtained a normal response in the right foot with a Babinski response in the left ; one year later the response on the right had become a Babinski response. To be set over against these variations, there was the typical Babinski response ipsilaterally following 30 divisions of the tract in the cord.

Further information can be obtained—as has been mentioned above—from that literature

where the sign was mentioned *en passant* and where necropsy and histological evidence was available. This material will be divided into three groups : (1) cases with severe lesions of the cortico-spinal tracts and with the Babinski response ; (2) cases with severe lesions of the cortico-spinal tracts and with the normal response ; (3) cases with normal cortico-spinal tracts and with the Babinski response.

(1) It may seem curious to start this list with a case reported by Babinski himself. For this is a list of those cases found in the literature in which the authors did not pay attention to the correlation of the histological lesion and the plantar response. Yet in 1902 Babinski and Nageotte reported the case of a syphilitic with multiple gummata and thrombosis of the basilar artery. There was a Babinski response on the right ; " le faisceau pyramidal est altéré dans toute la hauteur de la moelle ". Babinski did not realize that this was the first evidence he had brought forward that his sign was related to a disturbance of the pyramidal tract.

In 1903 Marie and Guillain reported a case with an enormous lesion of the left hemisphere in the distribution of the middle cerebral artery ; there was a contralateral Babinski response. Lewandowsky (1905) reported a similar case with a lesion affecting the whole cortico-spinal tract ; here again there was a contralateral Babinski response. Kattwinkel (1907) reported a case with bilateral Babinski responses associated with bilateral cortico-spinal sclerosis. Gierlich (1910) reported a case of monoplegia due to a cerebral thrombosis ; the cortico-spinal tract was degenerate and there was a Babinski response. Davison, Goodhart, and Savitsky (1935) reported a case of occlusion of the left superior cerebellar and left middle cerebral arteries ; there was demyelination of the cortico-spinal tract and the patient had shown a Babinski response. Davison in 1937 reported two cases of occlusion of the uppermost portion of the anterior spinal artery ; both had Babinski responses with involvement of the cortico-spinal tracts. Putnam in 1940 introduced the operation of cutting the lateral cortico-spinal tract as therapy for Parkinsonism ; he obtained a Babinski response. In 1944 Davison reported two further cases of thrombosis of the anterior spinal artery in the medulla ; they also showed involvement of the cortico-spinal tracts and Babinski responses. In 1954 Siekert and Sayre reported a case of thrombosis of the basilar artery ; at necropsy they found a large lesion involving at least half the pons, including its medial part ; it undoubtedly destroyed the great majority of the cortico-spinal fibres ; there was a bilateral Babinski response.

(2) In 1907 Roussy published two cases in which there was no Babinski response ; in both of them there was degeneration of the cortico-spinal tract.

(3) In 1929 Mathieu and Bertrand published their classical paper on cerebellar degenerations. It contains the following two cases. In the case of Mme. Lec. there was " un état de contracture et d'hypertonicité généralisée, mais prédominant aux membres inférieurs " ; on the right there was a Babinski response and on the left there was also a Babinski response, but it was " moins nette " ; histological examination showed : " Les voies pyramidales directes et croisées sont intactes, sauf une atteinte légère à droite du segment antero-externe de la voie pyramidal croisée ", in the cord ; in the peduncle the cortico-spinal tracts were normal. In the case of Mme. Quer. both plantar responses were of the Babinski type ; both cortico-spinal tracts were normal throughout.

In 1938 Waggoner, Löwenberg, and Speicher, reported a case of hereditary cerebellar atrophy. " There was a Babinski response bilaterally . . . the pyramidal tracts, both direct and crossed, were well-preserved."

Lassek (1945) has also reviewed the subject of the Babinski response. He collected cases reported in the *Archives of Neurology and Psychiatry* (Chicago), the *Journal of Nervous and Mental Disease*, and *Brain*, but he had no post-mortem evidence of the nature of the lesions.

Finally, it is essential to know whether the Babinski response ever occurs in the normal. Babinski wrote that abduction of the toes can occur in the normal ; he believed that extension of the big toe never occurs in the normal. This question may now be regarded as settled by Davidson (1931), Yakovlev and Farrell (1941), and Morgenthaler (1948). Davidson examined 130 adults under usual clinical conditions. He came to the conclusion that " extension of the toes, even of the big toe, is compatible with a normal motor system ", but what is pathological is " isolated extension of the big toe with fanning of the other toes ". Yakovlev and Farrell examined soldiers before and after marching 14 miles : 7·2% of them developed extension of the big toe on one side, 1·2% bilaterally. One conclusion from this paper, which the authors do not draw, is that isolated extension of the big toe is an insufficient index of abnormality. It is for this reason that many neurologists speak of the Babinski response only when there is extension and fanning of all toes.

Morgenthaler (1948) examined 200 schoolchildren taken off a playground. He found that extension of the big toe alone occurs in 1·5% (±0·5), and spreading of the toes occurs in 7·5% (± 2·5). He agreed with

Davidson that the combination of extension of the big toe with fanning of the other toes never occurs in the normal.

If we now sum up the findings from the literature, the following facts become clear :—

(1) Babinski did not at first claim that his sign indicated an anatomical lesion of the pyramidal tract.

(2) He at first claimed that it indicated a " perturbation dans le fonctionnement " of this tract. However, it is unclear what Babinski meant by the function of a tract. Within the present state of knowledge of the physiology of the nervous system, the term could only be vague when applied to any tract, unless it is clearly defined on each occasion ; in relation to the cortico-spinal tract, agreement would not be reached concerning the function of this tract. Further, if anatomical evidence does not show a specific relation between the cortico-spinal tract and the Babinski response, there is no basis for the conjecture that there is a physiological relation between the type of response and the function of the tract.

(3) Babinski knew that his sign could be absent when the spinal cord was totally divided. He never stated that complete removal of the influence of the cortico-spinal tract does not necessarily give his sign. Although this removes the validity of his original statements, he never retracted them.

(4) Extension of the toes, even of the big toe, on plantar stimulation, is compatible with a normal motor system ; isolated extension of the big toe with fanning of the other toes is an abnormal sign, and indicates abnormality of the central nervous system.

(5) Cases have been reported in which there were histological lesions of the cortico-spinal tract and in which there was no Babinski response.

(6) In cases of complete division of the cord, there may be a normal plantar response, a Babinski response, or various forms of plantar response. Moreover, the kind of response may change with time ; it often changes within a few days of the infliction of the lesion, and within a few days of death ; but it may change also weeks or months after the infliction of the injury and weeks or months before anaemia, uraemia, or death arrive.

(7) The Babinski response may appear in normal people during hypoglycaemia, during general anaesthesia, and after the injection of hyoscine ; it can occur in epileptics during or after the fit ; it can occur in the normal during sleep.

All these satisfactorily established facts, although some of them are well known to neurologists, do not seem to have entered the corpus of medical or neurological teaching. It can be pointed out, however, that there never has been a correlation of this sign with histological evidence of the state of the central nervous system performed in an adequate number of cases. To fill this gap, we present our evidence.

NEW OBSERVATIONS

Material and Methods

The material of this investigation consists of patients examined before and after operations on the spinal cord. After death, the brains and cords were removed and examined histologically. Transverse sections of the cords in the region of the operation are presented here in the form of diagrams. The reasons for showing diagrams rather than photographs are the ease with which one case can be compared with another, and the fact that in some cases the angle made by the knife at operation is not a right angle to the long axis of the cord, and so no true view of the maximal area of damage is given by one photograph. The case numbers are those used throughout our series of cases, and so the diagrams may be compared with photographs of the cords given in our other papers. A photograph of a transverse section from the lumbar cord of one case from each group has been included, to show the extent of the descending degeneration.

All the patients whose cords are shown died from cancer ; in none of them did the cancer involve the central nervous system. A control group of eight patients dying of cancer was also examined during life and after death histologically ; none of these patients had abnormal plantar responses and none of them showed degeneration of tracts in the cord. Being normal in all the respects that concern us here, the patients of this control group will not be mentioned again. All the patients of the main series had various forms of cordotomy designed for the relief of pain. The operations were performed by various neurosurgeons working in London ; most of them were done by Mr. Wylie McKissock. It is to be stressed that for the relief of pain the lesions are not usually made of such an extent as some of those shown here. The cases with most extensive lesions are relevant to the subject under consideration, and it is particularly these cases that are presented here.

This material can be used only to answer questions concerning the relation of the plantar response to histologically demonstrable changes in the tracts of the spinal cord. No lesions of tracts in the brain have been included, and no reference is made to cases of total transverse cord lesions.

In all patients, the observations on the plantar responses were made before and after cordotomy ; thus the observations during the period before the operation form a control for the type of plantar response observed after operation. All the observations were made by one person. The patients were examined when they were warm in bed. They were lying on their backs with the trunk slightly flexed, and the lower limbs slightly flexed

at the hips, and loosely extended at the knees. One hand of the examiner was placed on the dorsal surface of the ankle, while the other manipulated the instrument for stroking the plantar surface. No force was applied to the knee to prevent it flexing, if this tended to occur. The instrument used was a Yale key or the writing end of a pencil. It was dragged along the plantar surface of the foot from the lateral part of the heel, along the lateral part of the plantar surface of the foot, stopping at the metatarsal head of the little toe. The plantar response was regarded as normal when there was flexion of the big toe, with or without flexion of the other toes. The plantar response was described as the Babinski response when there was extension of all the toes, with at least a slight degree of fanning. Variations and other observations on reflexes will not be given here ; for the purpose of this paper is to correlate the lesion in the central nervous system with the sign as elicited by clinicians during their routine examination of patients. The kind of response found during the first 24 hours after the operation and during the period when the patient was clearly moribund will not be mentioned ; thus the plantar response given here is that found between these episodes. This period after the operation and before death varied between three weeks and 14 months. In all cases shown here, histological examination of the spinal cord and brain was carried out ; and so the exact extent and position of the lesion are known.

Results

In the diagrams the area blocked in represents the maximal area of damage ; it is the area of the operation, and shows the extent of the lesion made by the knife. In this area there are no normal fibres ; the region left unshaded is normal histologically. The material is divided into six groups.

Group I : Babinski Response.—This group contains those cases where there was the typical Babinski response and damage to the lateral cortico-spinal tract. The operation areas are shown in Fig. 1 in Cases 5, 53, 34, and 22. The descending degeneration in the lumbar region in Case 5 is shown in Fig. 7. In these patients, the plantar response remained the typical Babinski response from 48 hours after the operation till death.

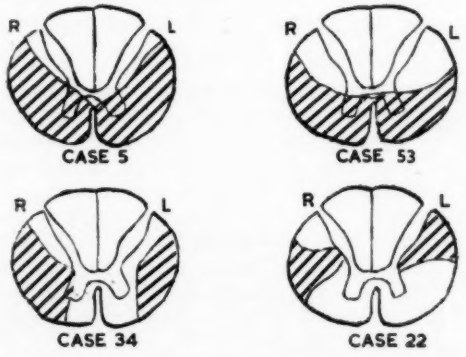


FIG. 1.—Diagrams of operation areas of spinal cords of patients showing the Babinski response.

Group II : Normal Response.—This group contains those bilateral cases where the plantar response was consistently normal for several weeks after the operation. From this group it can be seen how extensive a lesion of the cord can be and normal plantar responses be retained. The operation areas are shown in Fig. 2 in Cases 4, 10, 1, 6, and 3 ; in Case 6 the lesion involved the lateral cortico-spinal tract on both sides. It is striking how similar the lesion was on the two sides, and yet on the left there was a normal plantar response and on the right there was the Babinski response. Case 3 is the most striking in this group, for the lesion involves a great deal of the lateral cortico-spinal tract. This is amply confirmed by tracing descending degeneration, yet the plantar responses remained normal for four and a half months after the operation ; they changed to the Babinski type 14 days before death. The descending degeneration in the lumbar region in this case is shown in Fig. 7.

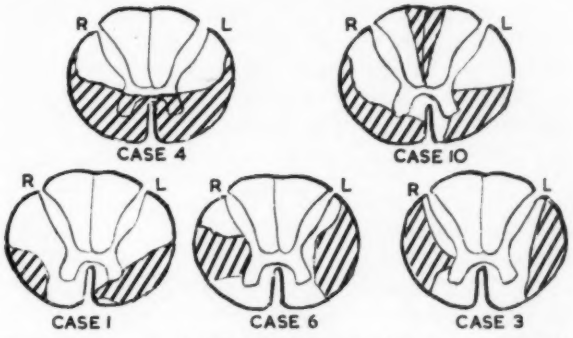


FIG. 2.—Diagrams of operation areas of spinal cords of patients showing the normal plantar response.

Group III : Babinski Response.—In this group are placed three selected bilateral cases in order to bring out further points. In these patients the plantar response was persistently of the Babinski type. The operation areas are shown in Fig. 3. In Case 52 it will be seen that the lesions are not large and that not much of the lateral cortico-spinal tract has been involved. In Case 33 it will be seen

FIG. 3.—Diagrams of operation areas of spinal cords of patients showing the Babinski response.

that the lesion scarcely involves the lateral cortico-spinal tract. In Case 19 the response was persistently of the Babinski type on both sides for the survival period of four months. The slight amount of descending degeneration in the region of the lateral cortico-spinal tracts in Case 33 is shown in Fig. 7.

From this group we see that the Babinski response can be associated with histological lesions which scarcely involve the cortico-spinal tracts.

Group IV: Varying Response.—In a fourth group are placed two categories of bilateral cases: those in which the plantar response was neither normal nor of the typical Babinski type and those in which the type of response changed during the period of survival. The operation areas are shown in Fig. 4. In Case 7 at first the plantar response on

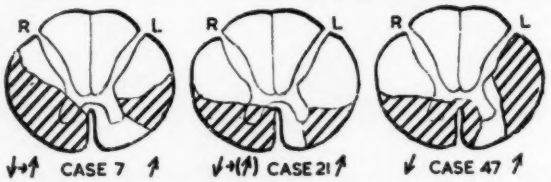


FIG. 4.—Diagrams of operation areas of spinal cords of patients showing varying plantar response.

the right was normal, but after 10 days it changed to the Babinski type. In Case 21 at first the response on the right was normal and there was no response on the left; 44 days after the operation the response on the right became diminished, and there was definite extension of all the toes but no fanning; that on the left was the Babinski response. The descending degeneration in this case is shown in Fig. 7. In Case 47 at first the response on the right was normal, although it needed firmer pressure than usual to bring it out; the response on the left was of the Babinski type.

Group V: Normal Response.—In this group is placed a selection of cases with large unilateral lesions. In all the patients the plantar response was normal. The operation areas of Cases 37, 39, 40, and 44 are shown in Fig. 5; it will be noted that in the latter the anterior cortico-spinal tract is completely divided. In this group it is seen that all the lesions are large. In Case 37 the lesion is so deep that it involves the grey matter and also extends posteriorly so as to involve the anterior part of the lateral cortico-spinal tract. The descending degeneration in this case is shown in Fig. 7. From this group we see that large unilateral lesions, involving part of the lateral cortico-spinal tract and the entire anterior cortico-spinal tract, may be associated with a normal plantar response.

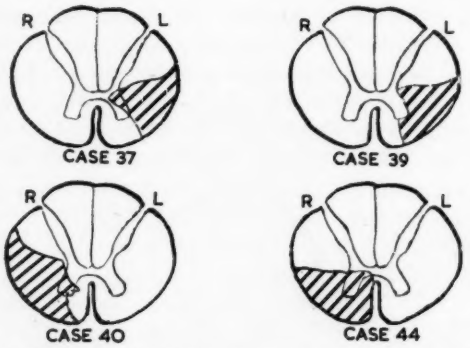


FIG. 5.—Diagrams of operation areas of spinal cords of patients showing normal plantar response.

Group VI: Two Operations.—Two patients are placed in this group, as both had two cordotomies; at first one side of the cord was operated on and later the other side. The results of these two operations on the plantar responses were unexpected. The operation areas are shown in Fig. 6;

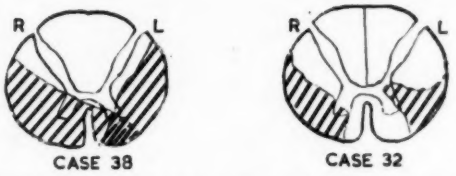


FIG. 6.—Diagrams of operation areas of spinal cords showing changing plantar responses.

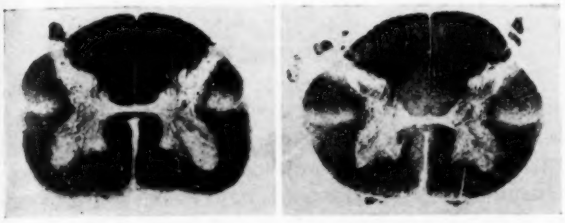
relevant parts of the history of these two patients follow.

Case 38.—After the operation on the right side of the cord, the left plantar response became of the Babinski type, whereas the right was more like the normal than like the Babinski response, although the toes did not readily plantar flex. But within a fortnight the left plantar response had become normal, and the right had changed definitely to the Babinski response. The left plantar response remained normal, until all response was rendered impossible owing to carcinomatous involvement of the sciatic nerve. Following the second operation, this time on the left side of the cord, the right response changed from the Babinski type to the normal.

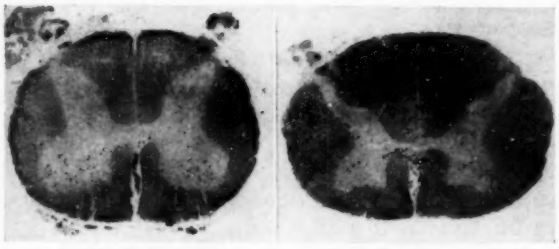
Case 32.—After the operation on the right side of the cord, both plantar responses were normal. However, 14 days after the second operation had been done on the left side of the cord, the right plantar response changed to the Babinski type, and remained of this type till the patient's death. The left remained normal, until it eventually became unobtainable due to involvement by cancer of the peripheral nerves in the left wall of the pelvis. There was no involvement of the nerves running to the right lower limb. The descending degeneration in this case is shown in Fig. 7.

The fact that after an operation on one side of the cord the plantar response on the other side changed to

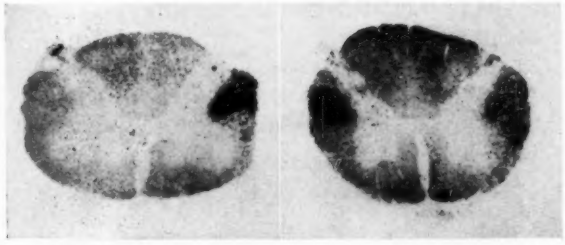
the Babinski type for a fortnight may indicate that the amount of trauma involved is enough to cause the response to be of the Babinski type. But when the tissue reaction has subsided, that is to say, 14 days after the operation, the plantar response of the operated side changed to the Babinski type. This response became normal after the opposite side of the cord had been incised.



Case 5 (Group I) Case 3 (Group II)



Case 33 (Group III) Case 21 (Group IV)



Case 37 (Group V) Case 32 (Group VI)

FIG. 7.—Photographs of transverse sections of the lumbar cord taken from one case in each group. In Cases 5 and 3 the photographs are from Weigert Pal preparations, in all the other cases they are from Marchi preparations.

It is clear that lesions of the spinal cord may or may not cause a Babinski response. From cases like Case 32 and Case 38, it seems that conclusions regarding the actual tract involved by a lesion cannot be drawn from the form of the plantar response.

Conclusions

From our evidence we are led to conclude that the Babinski response may accompany large lesions of the anterior half or more of the cord, the lateral cortico-spinal tracts remaining intact. It may also accompany total lesions of the lateral cortico-spinal tract. Our evidence also leads us to conclude that the normal plantar response may occur with large lesions of the anterior half or more of the cord, and it may also accompany extensive lesions of the lateral cortico-spinal tracts.

If we go into further detail we note that small lesions, such as those shown in Fig. 3 (Case 52), or superficial lesions such as those shown in Fig. 3 (Case 33), may be associated with the Babinski response.

Although it may be surprising that such small anterior and antero-lateral lesions can be associated with the Babinski response, it is perhaps to be expected. For it is well known that this response can be caused by hyoscine, alcohol, fatigue, or cerebral anoxia. It is clear that it does not need much trauma of any kind to bring about this pathological response. Any operation on the cord might constitute such trauma. Indeed, we have had one case in which a bilateral Babinski response followed a unilateral cordotomy, and cases where, following an operation on one side of the cord, the Babinski response occurred on the opposite side of the body. Of greater interest perhaps are those cases in which there were persistently normal responses. Most extensive lesions of the cortico-spinal tract are shown in Fig. 2 (Case 3); this patient had normal plantar responses bilaterally for many months after the making of these lesions.

It is instructive to compare the lesions of the cases of the different groups. Thus the lesions shown in Fig. 1 (Case 34) are similar to those shown on the left side of Fig. 2 (Case 6) and the right side of Fig. 5 (Case 40); and yet in Case 34 there were always Babinski responses, and in Case 6 the response was always normal, and in Case 40 the response was normal for three months after the operation. Similarly the lesion on the right side of Fig. 1 (Case 53) is similar to that on the right side of Fig. 6 (Case 32), and yet in the former patient there was always a Babinski response and in the latter patient the response was normal for six weeks after the operation. It is striking to note how in Fig. 2 (Case 6) the lesion on the left side of the cord is more extensive and involves more of the lateral cortico-spinal tract than that on the right side of the cord; and yet the former lesion was associated with a normal plantar response, and the latter with the Babinski response. The lesions shown in Fig. 3 (Case 19) bilaterally were less extensive than those shown in Fig. 2 (Case 4); in the former patient there was a bilateral Babinski response and in the latter a normal response bilaterally. And the lesion shown in Fig. 3 (Case 52) on the left side was associated with a Babinski response whereas that

shown on the right side of Fig. 6 (Case 32) was associated with a normal response for several weeks.

Thus a comparison of the various lesions of this series lends little support to a belief that there is a particular relationship between the lateral cortico-spinal tract and the plantar response.

A comparison of the cases having unilateral lesions with those having bilateral lesions immediately shows the following: a unilateral lesion can be large and associated with a normal plantar response whereas a small bilateral lesion may be associated with the Babinski response.

It is certainly necessary to justify the taking out from the gamut of signs one particular reflex response and discussing it divorced from the other manifestations of neurological functioning. The reason for doing this is that this sign is often used just in this manner. When the response is the Babinski response, physicians are accustomed to believe that there is a disorder (if not a gross anatomical lesion) of the cortico-spinal tract, and when the plantar response is normal they are ready to assume that the cortico-spinal tract must be normal.

The plantar response was considered by Fulton and Keller (1932) in great detail in their book *A Study of the Evolution of Cortical Dominance in Primates*. They came to the conclusion: "It is justifiable to conclude that in the higher primates the sign of Babinski is associated with isolated destruction of the pyramidal pathways." In view of our evidence we cannot support this statement. We would say: "The Babinski response may be associated with no histological lesion, or it may be associated with lesions in many parts of the spinal cord." Fulton and Keller continue: "There are cases in the literature in which the sign was said to be present in the absence of injury to the cortico-spinal pathways, but in none of these instances has there been decisive anatomical evidence of the integrity of the pyramidal system." We would like to suggest that this series of proved lesions has now provided such anatomical evidence.

It is well established that the normal plantar response can occur in total division of the spinal cord; experience has also taught one that even if the normal response is not obtained, other forms of plantar response, which are not the Babinski response, are often found in such cases. A spinal cord, or the caudal part of a spinal cord, which is functioning independently, cut off from its normal relation to the rest of the central nervous system, may not be compared to a spinal cord in which certain tracts are divided and other tracts intact. To regard the Babinski response as a spinal reflex whose manifestation is prevented by the functioning of one, and only one, descending tract, is an over-simple conception of neurophysiology.

SUMMARY

An account is given of Babinski's contributions to the study of the normal plantar response and the response named after him.

The literature correlating the normal plantar response and the Babinski response with the state of the cortico-spinal tract (as shown histologically) is reviewed and summarized.

A correlation of the plantar response with proved lesions of the spinal cord is presented. This material consists of 38 cases of antero-lateral cordotomy.

It is concluded that any lesion of the lateral and ventral columns of the cord may, or may not, cause the Babinski response; that conclusions cannot be drawn with regard to the tract involved when the Babinski response is found; that the Babinski response is often found with histologically normal cortico-spinal tracts; that a lesion of one side of the spinal cord may be associated with a Babinski response on the opposite side of the body; that lesions of the anterior half of the spinal cord may accompany the Babinski response; that apparently identical lesions on the two sides of a spinal cord may be associated with a normal plantar response on one side and a Babinski response on the other; that small bilateral lesions of the cord are more likely to cause a Babinski response than large unilateral lesions.

This may be summarized by the statement: there is no particular relation between the anatomical state of the cortico-spinal tracts and the form of the plantar response.

The Babinski response is a pathological response; it may be taken as an indicator that there is an abnormality of function in the central nervous system.

Patients 4, 6, 19, 32, 33, 34, 37, 38, 39, 40, 44, and 47 were in the National Hospital. Their hospital case numbers were respectively 31751, 18299, 16162, 29786, 30036, 32673, 41002, 36799, 14334, 39150, 17537, and 35455.

We take this opportunity of expressing our gratitude to Mr. Wylie McKissock and to the other neurosurgeons for their cooperation and generosity.

Dr. E. A. Carmichael provided the facilities for this work and we wish to thank him for this and for his helpful advice.

Our thanks are due to the Medical Committee of the National Hospital for Nervous Diseases for allowing us to publish this series of cases.

We also wish to express our gratitude to Mr. Peter Sharp and Mrs. J. A. Mills for their excellent technical assistance.

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THE AUGUST (1955) ISSUE

The August (1955) issue contains the following papers :—

Tuberculous Meningitis of Acute Onset. K. B. Taylor, H. V. Smith, and R. L. Vollum.

The Pathological Effects Produced by Sera of Animals Immunized with Foreign Nervous or Splenic Tissue. Part I : Intracisternal Injection of Serum. E. Weston Hurst.

Spino-cortical Fibres in Man. P. W. Nathan and Marion C. Smith.

On the Muscular Rigidity and Hyperreflexia Due to Hypothermia in Man with Observations on the Accommodation of Peripheral Nerve. John A. Simpson.

Congenital Hereditary Vertical Nystagmus. W. I. Forsythe.

A Benign " Tumour " of the Cerebellum. D. R. Oppenheimer.

Dysphasia Following Right Temporal Lobectomy in a Right-handed Man. G. Ettlinger, C. V. Jackson, and O. L. Zangwill.

Impaired Identification of Faces and Places with Agnosia for Colours. C. A. Pallis.

Rauwolfia Serpentina (Serpasil) in Psychiatry. J. D. Glynn.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 12s. 6d.

J. Neurol. Neurosurg. Psychiat., 1955, **18**, 260.

THE PATHOLOGICAL EFFECTS PRODUCED BY SERA OF ANIMALS IMMUNIZED WITH FOREIGN NERVOUS OR SPLENIC TISSUE

PART II: INTRA-ARTERIAL INJECTION OF SERUM

BY

E. WESTON HURST

From Imperial Chemical (Pharmaceuticals) Limited, Hexagon House, Blackley, Manchester

In an earlier paper (Hurst, 1955) we have described the cerebral lesions which follow intracisternal injection in monkeys of the sera of goats immunized with simian brain, and have attributed them to an antigen-antibody reaction. The method of bringing the two components of the reaction into contact was, however, so " artificial " that it seemed improbable that it could throw light upon the genesis of lesions developing in animals immunized with nervous tissue, or of those obscure conditions in man in which sensitivity is believed to play a part. We therefore studied the effect of introducing the antisera into the blood-stream. Large amounts (10 ml.) injected into the general circulation caused no apparent disturbance and, even when injected directly into the common carotid artery while blood was flowing through the vessel, the sera produced no detectable macroscopic or microscopic reaction in the brain. If, however, the latter procedure was followed after ligation of all branches of the common carotid artery other than the internal carotid, very marked disturbances ensued. As previously, we compared the effects produced by neurotoxic sera with those evoked by an anti-spleen serum, as well as, of course, the (negligible) effects of normal goat serum.

Experimental

Preparation of Sera and Operative Technique.—The sera were prepared in the manner described earlier (Hurst, 1955) and were stored at —10° C.

In monkeys anaesthetized with nembutal, we tied all branches of the right common carotid artery with the exception of the internal carotid. The sera, thawed and re-centrifuged immediately before use and then warmed to 37° C., were injected slowly into the common carotid while blood flowed through the artery. The time taken for injection was two minutes for monkeys of the "C" series (Table) and five to eight minutes for those of the "H" series. After injection blood was allowed to flow through the artery for half-a-minute or so, before ligation of the vessel proximal to and distal to the needle puncture. If the animal survived it was sacrificed four to six days after operation.

A résumé of experiments performed appears in the Table.

Effects of Injecting Neurotoxic Serum

In many animals, during or immediately after the injection, there occurred more or less severe but transient movements of the diaphragm and abdominal wall, producing the effect of retching or of hiccough.

By the time the skin was sutured, or a few minutes later, the eyelids of the homolateral orbit began to swell; two monkeys (H4 and 7) receiving the smallest dose of serum, and one (H12) pre-treated with cortisone, provided the only exceptions to this statement. When death followed soon after injection, the brains of the animals showed the cerebral engorgement described below; thus the ocular manifestations, confined sharply to the area of distribution of the ophthalmic branch of the anterior cerebral artery, constituted outward and visible evidence of the reaction taking place within the cranium. With less severe reactions the eyelids were merely oedematous and the oedema disappeared within a day or so, usually leaving some residual difference in the palpebral fissures and in the size of the pupils due probably to disturbance of the sympathetic at operation. Other animals, however, showed " purple " oedema, with severe congestion and haemorrhages becoming more intense for many hours and persisting for several days or until death. The most extreme reaction occurred in H10 and led to complete destruction of the eyeball, the dry and shrunken remnants of which six days later were surrounded by cicatrizing but still oedematous orbital and palpebral tissues. Immediately after the operation many animals lachrymated vigorously, usually from the homo-

TABLE

RÉSUMÉ OF EXPERIMENTS PERFORMED

Number of Monkey	Inoculum	Summary of Effects
	Anti-brain Goat Serum	
C3	10 ml.	Intense " purple " oedema of homolateral orbital region. Death two hours after injection. Many areas of purple discoloration of homolateral cerebral hemisphere
H3	4 ml. + 6 ml. normal goat serum	As C3 but less severe. Death two hours later. Brain as preceding
H8	3 ml. + 7 ml. normal saline solution	" Purple " oedema of homolateral orbit. Killed five days after injection. No macroscopic changes in brain
C6	2 ml.	" Purple " oedema of homolateral orbit. Cardiac and respiratory failure. Revived. Oedema diminishing and general condition good when killed four days after injection. No macroscopic changes in brain
H9	2 ml. + 8 ml. normal goat serum	Intense " purple " oedema of homolateral orbit. Excessive salivation and temporary blindness on recovery from anaesthetic. Homolateral eyelids nearly closed and still purplish red, movements slow and clumsy, animal " weedy " when killed five days after injection. No macroscopic changes in brain
H23	1 ml. + 9 ml. normal goat serum	Oedema of homolateral orbit. Death three hours after injection. Areas of purple discoloration of homolateral cerebral hemisphere
H5	1 ml. + 9 ml. normal goat serum	Oedema of homolateral orbit. Recovered from anaesthetic and was well and active for 20 hours. Then suddenly became very ataxic and could not rise from floor of cage. At 48 hours respiration suddenly became very feeble. Killed when moribund 52 hours after injection. No macroscopic changes in brain
H7	1 ml. + 9 ml. normal goat serum	No apparent effect. Killed five days later. No macroscopic changes in brain
H22	1 ml. + 9 ml. normal goat serum + 10 mg. hyaluronidase	Oedema of homolateral orbit. Cardiac and respiratory failure. Revived. Oedema disappeared within 24 hours and animal apparently well when killed five days later. No macroscopic changes in brain
H4	1 ml. + 9 ml. normal saline solution	No apparent effect. Killed five days later. No macroscopic changes in brain
	Anti-brain Goat Serum in Monkeys Pre-treated with Cortisone	
H10	10 ml.	Severe " purple " oedema of homolateral orbit. Cardiac and respiratory failure. Revived. Recovered from anaesthetic with dilatation of contralateral pupil. Homolateral eye still closed at necropsy six days after injection. On dissection, contents of orbit still rather oedematous and stained with earlier haemorrhages ; eyeball shrunken and dry, and obviously destroyed completely as a functional unit. No macroscopic changes in brain
H12	5 ml. + 5 ml. normal goat serum	Death one hour after injection. Brain showed areas of purple discoloration
	Normal Goat Serum	
C5	10 ml.	Slight oedema of homolateral orbit. Oedema disappeared in two days and monkey apparently normal when killed four days after injection. No macroscopic changes in brain
H1	10 ml.	No apparent effect. Killed four days later. No macroscopic changes in brain
H2	10 ml.	As preceding but killed five days after injection
H17	10 ml.	Very slight oedema of homolateral orbit disappearing overnight. Otherwise as preceding
H16	10 ml. + 10 mg. hyaluronidase	As preceding
	Normal Monkey Serum	
H6	10 ml.	No apparent effect. Killed five days after injection. No macroscopic changes in brain
	Anti-spleen Goat Serum	
H21	2 ml. + 8 ml. normal goat serum	Oedema of homolateral orbit. Death two hours later. Areas of purple discoloration of homolateral cerebral hemisphere
H20	2 ml. + 8 ml. normal saline solution	Cardiac and respiratory failure. Revived. Complete recovery from anaesthetic. Twenty hours after injection severe epileptic fits passing into status epilepticus and death at 24 hours. Generalized congestion of whole brain
H13	1 ml. + 9 ml. normal goat serum	Severe oedema of homolateral orbit. Recovered from anaesthetic with apparent blindness, contralateral hemiplegia and hemianaesthesia. Oedema disappeared in course of three days, at which time impaired vision to left and left-sided paresis almost complete in arm. When killed five days after injection vision much improved. Brain showed large and small softenings.

continued

Table continued

Number of Monkey	Inoculum	Summary of Effects
	Anti-spleen Goat Serum	
H19	0·7 ml. + 10·3 ml. normal goat serum	Oedema of homolateral orbit. Cardiac and respiratory failure. Revived. On recovery from anaesthesia, contralateral pupil greatly dilated and vision defective to this side. Oedema disappeared within 72 hours, but visual changes persisted until necropsy on fifth day. No macroscopic changes in brain
H18	0·7 ml. + 10·3 ml. normal goat serum + 3 mg. hyaluronidase	Severe oedema of homolateral orbit. Cardiac and respiratory failure. Revived. On recovery from anaesthetic animal blind, left eye deviated to contralateral side (right eye not visible), contralateral hemiplegia and hemianaesthesia. Oedema, blindness, and deviation of eye disappeared in 48 hours. Generalized tremor on movement and hemiparesis persisting at necropsy five days after injection. Brain showed small and large softenings.
	Anti-spleen Goat Serum in Monkeys Pre-treated with Cortisone	
H11	10 ml.	Reddening but no oedema of homolateral orbit. Cardiac and respiratory failure. Revived. No recovery of consciousness. Death seven hours after injection. Areas of purple discoloration of homolateral cerebral hemisphere
H14	3 ml. + 7 ml. normal goat serum	Oedema of homolateral orbit. Death one hour after injection. Brain as preceding

lateral eye, but once from the contralateral and once from both.

Over a period extending from within a few minutes to several hours after the operation, injected monkeys were very prone to sudden cardiac and respiratory failure and death. In several instances in which we countered impending collapse with intravenous or intracardiac adrenalin coupled with artificial respiration, we succeeded in preventing apparently certain death ; on other occasions the treatment was of no avail.

On the day after injection of serum, several animals receiving small doses appeared normal. One (H9), however, which had been temporarily blind and had salivated vigorously on coming round from the anaesthetic, ate little food for 48 hours and remained slow and clumsy in all its movements until necropsy on the fifth day. A second (H5), apparently quite well until 20 hours after injection, then suddenly developed progressive nervous symptoms and was moribund at 52 hours. It is worth recalling that we have described similarly delayed and progressive symptoms as a sequel to chemical anoxia (Hurst, 1940, 1942).

Animals dying within an hour or two all exhibited areas of reddish or purple discoloration within the territories of the anterior and middle cerebral arteries of the homolateral cerebral hemisphere. On section the grey matter was intensely congested, the white matter less obviously so, though to some extent the congestion here was probably merely obscured by the whiteness of the areas. Animals killed two to six days after injection showed no certain macroscopic changes in the brain.

In one monkey, the addition of hyaluronidase to the serum in the hope of enhancing capillary permeability did not apparently increase the severity of the effects. In two monkeys pre-treatment with 10 mg./kg. cortisone 24 and two hours before operation may have modified slightly the reaction, but certainly did not prevent it. We received the impression that the effects of a given dose of serum diluted with physiological saline were less severe than those of an equivalent dose diluted with normal goat serum.

Pathological Examination.—Fig. 1 depicts the macroscopic appearances in the brain of C3 which died within two hours of the injection of serum. Intense purple discoloration, accompanied by considerable swelling, affected part of the basal surface of the homolateral frontal lobe and the temporal pole, extended on to the lateral surface where it missed the pre- and post-Rolandic convolutions, and reached the vertex in the hinder parietal area. This general distribution appeared to be fairly constant and corresponded with that of microscopical changes in the monkeys which survived. Much of the homolateral brain and the whole of the other side were free from congestion.

Animals killed after four to six days did not show clear macroscopic abnormality.

Microscopical examination in animals dying within one to three hours (C3, H3, 12, 23) showed every vessel, large and small, in the affected areas to be stuffed with erythrocytes (Fig. 2). In the arteries and arterioles for the most part these appeared as discrete units, but in the more severely affected regions those in the capillaries tended to lose their outlines and fuse into rather granular plugs which still preserved the usual staining properties of red blood cells. Lying between the adventitia and the nervous substance outside many of the arteries and venules was a hyaline coagulum which stained metachromatically with toluidin blue. Occasional capillary or ball or ring haemorrhages were seen,

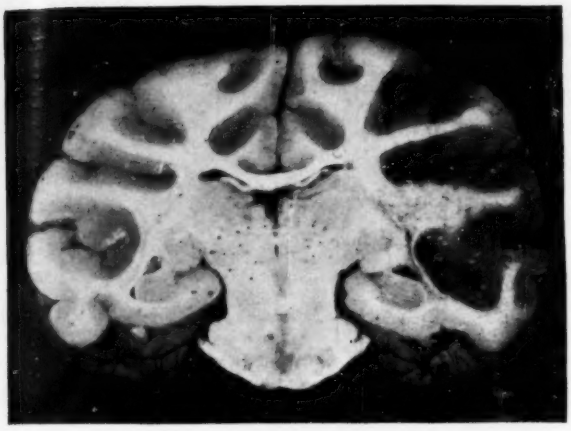

FIG. 1.—Intense congestion of some cortical areas two hours after intra-arterial injection of neurotoxic goat serum.

but were not a conspicuous feature. Even at two hours after injection the oligodendroglial cells in affected areas already exhibited pyknosis of the nuclei and acute swelling of the cytoplasm, and the nerve cells vacuolation of the cytoplasm and pericellular oedema.

Despite the absence of macroscopic alterations, several of the monkeys surviving longer showed lesions in the general areas outlined above.

In H5 and H9 these were numerous and often severe, particularly in the cortex of the gyri temporalis superior and inferior at the temporal pole and on the anterior part of the lateral surface of the temporal lobe ; further back in these gyri lesions more characteristically involved the white matter rather than the cortex and also affected the gyrus angularis, and in minor degree the gyrus centralis posterior, both in the present monkeys and in those to be described in a later section. Smaller areas of less severe damage occurred in adjacent parts of the cortex, in the nucleus amygdalae, in parts of the caudate and lenticular nuclei, in the wall of the third ventricle and subthalamic nuclei, and in the optic tract. The more severe lesions consisted in complete necrosis of the cerebral cortex over areas varying from pinheads to those of 0·5 cm. or more in diameter. In these areas many capillaries were still blocked by the granular plugs derived from altered red blood corpuscles, but ordinary thrombi were not seen ; the capillary endothelial cells in many cases were necrotic. In the case of longer duration (H9), the less severe lesions in the grey matter were characterized by moderate to severe vacuolation of nerve cells, sponginess of the ground substance, ballooning and fragmentation of myelin sheaths, formation of plasma-rich and often binucleate glial cells, early reaction on the part of the microglia, and swelling and proliferative activity of vascular adventitial or endothelial cells. The hyaline coagulum outside certain vessels had been resolved into globules which were undergoing phagocytosis. The white matter of the gyrus temporalis superior in its middle and posterior parts showed considerable pallor and swelling, as compared with the corresponding area of the opposite side ; the arcuate fibres were less affected than the rest (Fig. 3). The myelin sheaths were separated by oedema and many were ballooned or fragmenting, while the neuroglial cells were enlarged and often binucleate and the microglia in an early stage of reaction. No fat was detected. This picture is very similar to that described by Greenfield (1939) in cerebral oedema. In the central parts of the optic tracts, small foci of ballooning or breakdown of myelin and of complete or almost complete softening often co-existed in the same section. In H5 similar lesions were at a less advanced stage of evolution. It is to be noted that in regions of damage short of complete necrosis the vessels were all normally patent ; if therefore they had suffered obstruction from the erythrocytic plugs mentioned

FIG. 2.—The microscopical picture corresponding to Fig. 1 as seen in a section stained by Weil's stain for myelin.

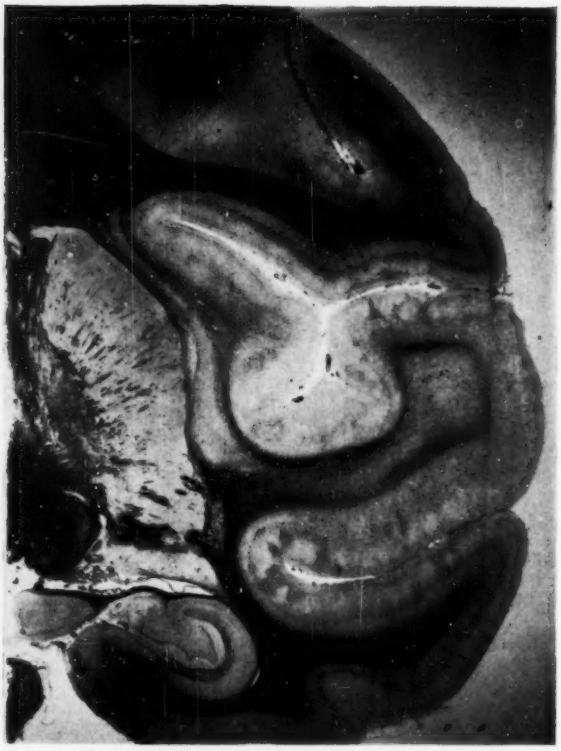

FIG. 3.—Oedema and demyelination in the white matter of the gyrus temporalis superior five days after neurotoxic serum. Lesions can be discerned also in the adjacent cortex and in the optic tract. Weil's stain.

above, these plugs had later been dislodged and the circulation re-established.

Similar but much less extensive and severe lesions obtained in C6 and H10, while only the optic tract was involved in H8. No nervous lesions were detected in H4, 7, and 22.

Although as stated previously, in the hours following the injection of serum, the " purple " oedema of the eyelids seemed to be a general indicator of the state of affairs within the cranium, the course of events in the brain and the eye did not necessarily run completely parallel. Thus H5 with severe nervous lesions suffered but moderate oedema of the eye, while H10 with comparatively mild cerebral changes showed extremely severe orbital destruction. In H10 the optic nerve was completely necrotic, as was the retina ; the former was devoid of any recognizable cellular remains, but in the latter large numbers of invading polymorphonuclears, also necrotic, could be discerned. Other nerves lying within the highly oedematous orbit were less severely damaged or were normal ; there was, however, extensive necrosis of fat and muscle, with lively proliferation of sarcolemmal nuclei and cells of the vascular adventitia in some places and no cellular reaction whatsoever in others. Although a minority of vessels appeared to be plugged with agglutinated red cells many seemed to be patent. Lumsden (1950) has described necrosis of the globe of the eye following the introduction of minute emboli into the carotid artery.

Effects of Injecting Normal Sera

Five monkeys, receiving very large doses of normal goat serum, with or without hyaluronidase, either suffered no obvious ill-effects (H1 and 2) or, after slight retching during the injection, developed very transient and slight orbital oedema which was never " purple ". At necropsy four to five days later the brains appeared normal.

One monkey receiving a large dose of normal monkey serum manifested no ill-effects.

Pathological Examination.—No microscopic changes were found in the brains of these animals.

Effects of Injecting Anti-spleen Serum

At any given dose this serum produced more severe effects than did the neurotoxic serum.

Oedema of the orbit, though not " purple ", was often severe. Two monkeys surviving the immediate effects of the injection recovered from the anaesthetic apparently blind. Residual symptoms included tremor on movement, and contralateral hemianopia, hemiparesis, and hemianaesthesia. One animal apparently well for 20 hours then developed convulsions and died at 24 hours in status epilepticus.

At necropsy on animals dying acutely, areas of purple discoloration were seen in the homolateral cerebral hemisphere. The brain of the monkey dying of convulsions at 24 hours was generally congested. At necropsy on cases surviving five days, two of three monkeys showed macroscopic softenings in the homolateral cerebrum ; these varied from purple pin-heads in parts of the cortex to extensive softenings (up to 1 cm. $\times$ 0·75 cm.) in the cortex, basal nuclei, or white matter. Haemorrhages were more frequent than with the neurotoxic serum.

Hyaluronidase did not appear to augment the damage, nor pre-treatment with cortisone appreciably to mitigate it.

Pathological Examination.—The microscopical changes in monkeys which succumbed within a few hours were indistinguishable from those following administration of neurotoxic serum. At seven hours (H11), in addition to the changes already mentioned, the capillary endothelial cells were pyknotic or apparently missing from the most severely affected areas.

In animals surviving longer, lesions were larger, more severe, and occurred over a wider area than with neurotoxic serum.

H20, dying in status epilepticus after 24 hours, showed generalized congestion of the brain with more intense congestion, capillary plugging, and incipient necrosis in the homolateral superior temporal gyrus, lenticular nucleus, etc.

H13, 18, and 19, killed on the fifth day, exhibited very severe and widespread softenings with more numerous haemorrhages than obtained in the neurotoxic group. All the areas previously mentioned as affected were more severely involved and, in addition, the internal capsule, anterior commissure, optic thalamus, centrum semi-ovale, and some areas of the cortex not previously observed to be damaged, e.g., the gyrus hippocampi, were here affected. The internal capsule particularly was the site of multiple severe injuries in H13 and 18, a fact reflected in the symptomatology during life. In parts of the white matter undergoing rapid and complete necrosis we made an observation previously recorded in chemical necrosis of the white matter (Hurst, 1940, 1942), namely that in these severely stricken areas the myelin sheaths quickly lose their ability to stain by Weil's method while retaining their normal form and contour, whereas in areas of partial damage the tinctorial properties are normal but the outline of the sheaths is grossly altered by beading, ballooning, etc. The optic tracts and nerves were severely damaged in all, but the retina was destroyed only in H19 and in none of the monkeys were the orbital changes nearly as severe as in H10.

The lesions caused by the anti-spleen serum were thus quantitatively more severe than those produced by anti-brain serum, but, using the intra-arterial route of injection, we were unable to detect any qualitative difference in the two series.

Comment

The injection into the cerebral circulation of anti-sera to either brain or spleen apparently damages the walls of the capillaries and may lead to intense congestion in territories (including the orbit) supplied by the arteries concerned. Where damage is most severe, we find the small vessels lastingly obstructed with granular plugs consisting of altered red blood cells, and full necrosis occurs in the surrounding nervous and orbital tissues. Where damage is less severe, we may suppose either that obstruction is temporary and that the circulation is later restored with only moderate injury to the nervous tissues, or that these suffer as a result of altered permeability or other change in the vessels ; in either case the ensuing lesions fall short of full necrosis. The former explanation of the genesis of this partial damage seems the more convincing since the more toxic anti-spleen serum, though certainly coursing through the same vascular channels as the anti-brain serum, produced far more widespread softenings with many more lastingly blocked capillaries and fewer areas of partial damage. However this may be, the lesions bear an obviously vascular stamp, and those evoked by neurotoxic serum do not appear different, apart from their lesser severity, from those arising from the action of anti-spleen serum. Thus we failed to obtain evidence that a neurotoxic serum given by the intra-arterial route is capable of direct assault on the nervous tissues, or in more general terms that an antigen on one side of the blood-brain barrier is capable of reacting with antibodies on the other. Without making any assumption as to the nature and relative sites of hypothetical antigen and antibody in some acute nervous diseases of obscure origin in man, we had hoped to produce in the experimental animal a condition resembling (say) acute haemorrhagic leucoencephalitis. We were disappointed, and from this point of view the observations have only a negative value.

Summary

Anti-brain and anti-spleen goat sera injected into the common carotid artery of monkeys, after ligation of branches other than the internal carotid, produce serious lesions in the vascular territories concerned. Damage to the vessel walls results in intense congestion, and the capillaries may become lastingly obstructed by plugs of altered red blood cells. Ischaemic changes follow in the nervous tissues. The anti-spleen serum was the more noxious.

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THE PROJECTION OF THE MIDLINE AND INTRALAMINAR NUCLEI OF THE THALAMUS OF THE RABBIT

BY

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Electrophysiological studies have indicated that the nuclei of the midline and internal medullary lamina of the thalamus together constitute a functionally distinct system which may be of considerable importance in the maintenance and control of normal cerebral activity. Since most of the physiological observations on this system have recently been collated in the publication of the symposium on "Brain Mechanisms and Consciousness" (Council for International Organizations of Medical Sciences, 1954) a detailed review of the literature will not be given here. Suffice it to say that whereas each of the principal thalamic nuclei is related to a localized cortical area, stimulation studies have shown that the midline and intralaminar nuclei are capable of exerting widespread effects on the activity of the cerebral cortex. The normal pathways by which these effects are mediated are still obscure since it has long been known that these nuclei have no direct connexion with the neopallial cortex as they do not undergo retrograde cell degeneration even after decortication. That their projection is extrathalamic is, however, well established (Rose and Woolsey, 1943, 1949) and there is some evidence to suggest that they may be related to the corpus striatum (Stefens and Fortuyn, 1953 ; Powell and Cowan, 1954).

In view of the important functional significance attributed to these nuclei more precise information concerning their efferent connexions is desirable.

In the present work the projection of the individual elements of this group has been studied in the thalamus of the rabbit using the technique of retrograde cell degeneration after lesions in the rostral part of the cerebral hemisphere.

Material and Methods

Thirty-five rabbits of different ages were used in this study. In the earlier experiments lesions were placed in the basal forebrain areas by inserting through a trephine hole in the skull either a fine ophthalmic knife or an insulated electrode. In the later experiments the use of a stereotaxic instrument with a set of previously determined coordinates of the rabbit forebrain permitted more accurate placing of the lesions. The animals were allowed to survive for periods of one to three months after operation. The brains were removed and fixed in 70% alcohol and blocks containing the entire cerebral hemispheres were embedded in paraffin wax and sectioned coronally at 20 to 25 μ. Every fifth section was mounted serially and stained with methylene blue or thionine and every sixth section with activated protargol. In most of the experiments the lesions were confined to one side but in a few animals bilateral lesions were made, the appropriate hemisphere of the latter being indicated in the text by the suffix R. or L. A number of series of sections of normal brains stained with both thionine and protargol were available for comparison with the experimental material. Essentially four different types of lesion were placed. In the first series of experiments almost the entire rostral portion of the hemisphere in front of the thalamus was ablated. In the second group a variety of lesions were placed in the internal capsule and basal forebrain areas to determine the gross projection and pathway of the efferent fibres of the midline and intralaminar nuclei. In the last two groups an attempt was made to localize the projection of individual elements of this system by controlled ablations of the cortex on the medial surface of the hemisphere and by a series of overlapping lesions in the corpus striatum. In addition to representative experiments of these groups, a few experiments which serve to exclude some of the adjacent structures will be described.

In view of the different terminology which has been used by previous authors for the nuclei of the midline and intralaminar system a brief reference to the nomenclature used in this paper is necessary. With one exception it will be the same as that adopted in the previous study in the rat (Powell and Cowan, 1954) ; in accordance with the description of Gurdjian (1927) the cell mass immediately adjacent to the mamillo-thalamic tract was called the medio-ventral nucleus but in the present study on the rabbit we have followed Rose and Mountcastle (1952) in calling this the ventro-medial nucleus. On the other hand the term nucleus reuniens has been retained for the most ventral nucleus of the midline group which Rose (Rose and Woolsey, 1948 ; Rose and Mountcastle, 1952) terms the medio-ventral nucleus ; this same nucleus has been subdivided by Fortuyn (1950) into a paramedian and a submedial nucleus. The rhomboid nucleus is the name given to the group of deeply staining cells immediately dorsal to the nucleus

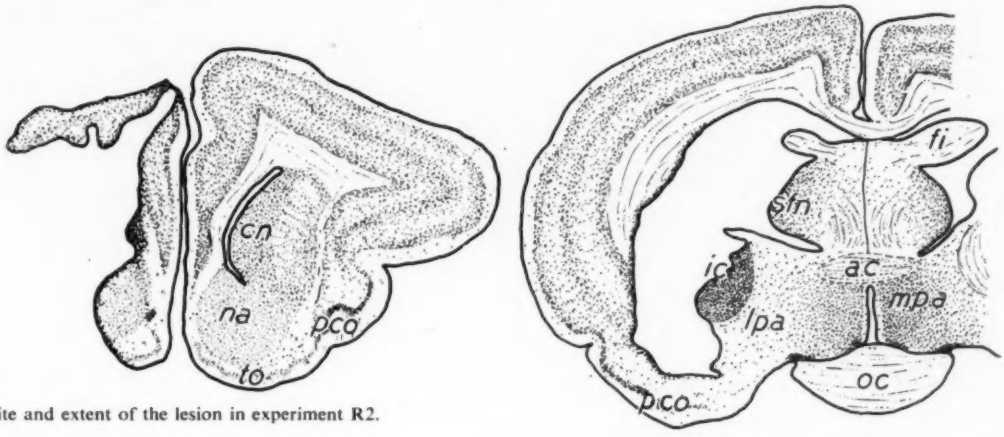


FIG. 1.—Site and extent of the lesion in experiment R2.

c n = caudate nucleus
n a = nucleus accumbens
t o = olfactory tubercle
p c o = pyriform cortex

s f n = septofimbrial nucleus
i c = internal capsule
l p a = lateral preoptic area
p c o = pyriform cortex
a c = anterior commissure
o c = optic chiasma
f i = fimbria
m p a = medial preoptic area

reuniens, the term n. centralis medialis referring to the midline cell mass between the two paracentral nuclei (cf. Rose and Woolsey, 1943). Since it is not possible to distinguish clearly between the parafascicular and centro-median nuclei either in normal or in the experimental material, these two elements will be described together simply as the parafascicular nucleus.

Results

In Rabbit 2, which is representative of the first group of experiments, the cerebral hemisphere was completely ablated in front of the genu of the corpus callosum. Examination of the serial sections shows that behind this level the lesion is somewhat less extensive, but with the exception of the neocortex on the dorso-lateral aspect of the hemisphere all the structures lateral to the anterior horn of the lateral ventricle have been destroyed, including the entire striatum, the anterior limb of the internal capsule, the lateral preoptic area, and the anterior third of the amygdaloid complex. The septum, i.e., the medial and lateral septal nuclei, the vertical limb of the diagonal band nucleus, and the anterior hippocampal cortex are intact. The medial preoptic and anterior hypothalamic areas have also escaped damage, since the lesion narrows considerably in its posterior part and is here confined to the body of the caudate nucleus and the immediately adjacent part of the internal capsule (Fig. 1). The retrograde cell degeneration in the thalamus is extensive and involves to a varying degree all the principal nuclei and most of the midline and intralaminar group (Fig. 2). Of the latter the nuclei reuniens, the rhomboideus, centralis medialis, paracentralis, centralis lateralis, and parafascicularis have undergone complete atrophy. The parataenial nucleus shows a severe cell loss throughout its antero-posterior extent and especially in the ventro-lateral two-thirds of its cross sectional area (Plate 1). The ventral vertical portion of the anterior paraventricular nucleus shows a definite loss of cells with shrinkage of the remaining cells but there is no appreciable change in the posterior paraventricular nucleus. In the anterior part of the reticular nucleus* there is a marked gliosis together with severe shrinkage and compacting of the cells and possibly some cell loss; posteriorly this nucleus shows little or no change. Of particular significance in the main thalamic nuclei is the complete retrograde degeneration of the nucleus ventralis anterior and the ventro-medial nucleus. With the exception of the antero-dorsal, the lateral and pretectal nuclei, and the medial and lateral geniculate nuclei, in all of which a small number of normal cells persist, the other principal nuclei are completely degenerate.

This and the other experiments in the group confirm the findings of Rose and Woolsey (1943) and our previous observations in the rat (Powell and Cowan, 1954) that the midline and intralaminar nuclei will degenerate following large lesions in the rostral telencephalon. The next group of experiments suggests that these nuclei project to the striatum and the adjacent neocortex and in their projection are largely independent of the principal

* As here used, the term reticular nucleus refers to the collection of cells in the external medullary lamina of the thalamus and does not refer to the brain-stem reticular formation.

f i = fimbria
h p = hippocampus
l = lateral nucleus
a d = antero-dorsal nucleus
a v = antero-ventral nucleus
p t = parataenial nucleus
r = reticular nucleus
v a = nucleus ventralis anterior
a m = antero-medial nucleus
a n = angular nucleus
s h = stria habenularis
p v = paraventricular nuclei
r e = nucleus reuniens
r h = nucleus rhomboideus
v b = ventro-basal nucleus
v m = ventro-medial nucleus
c l = nucleus centralis lateralis
p c = nucleus paracentralis
m d = medio-dorsal nucleus
c m = nucleus centralis medialis

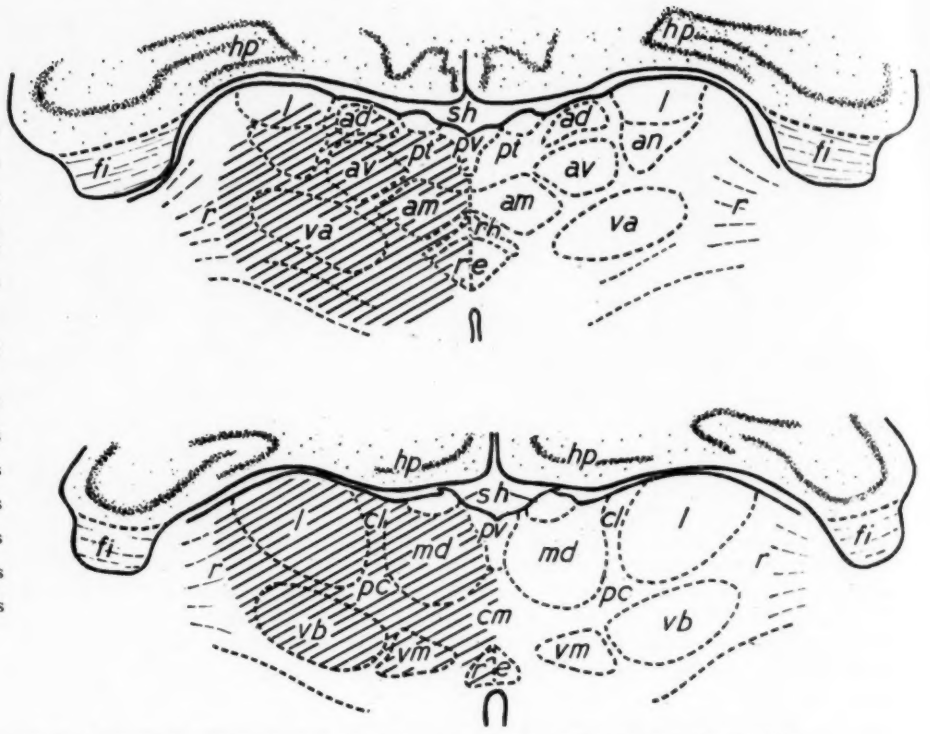


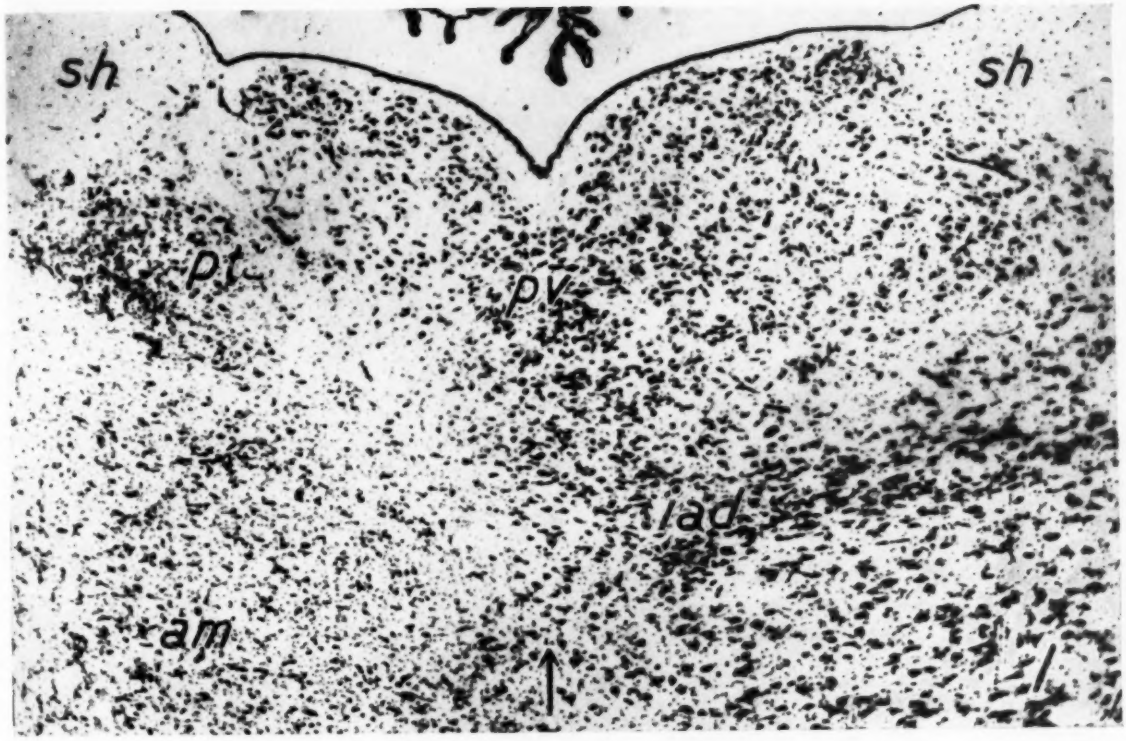
FIG. 2.—The extent of the retrograde degeneration in the thalamus in experiment R 2 (indicated by hatching).

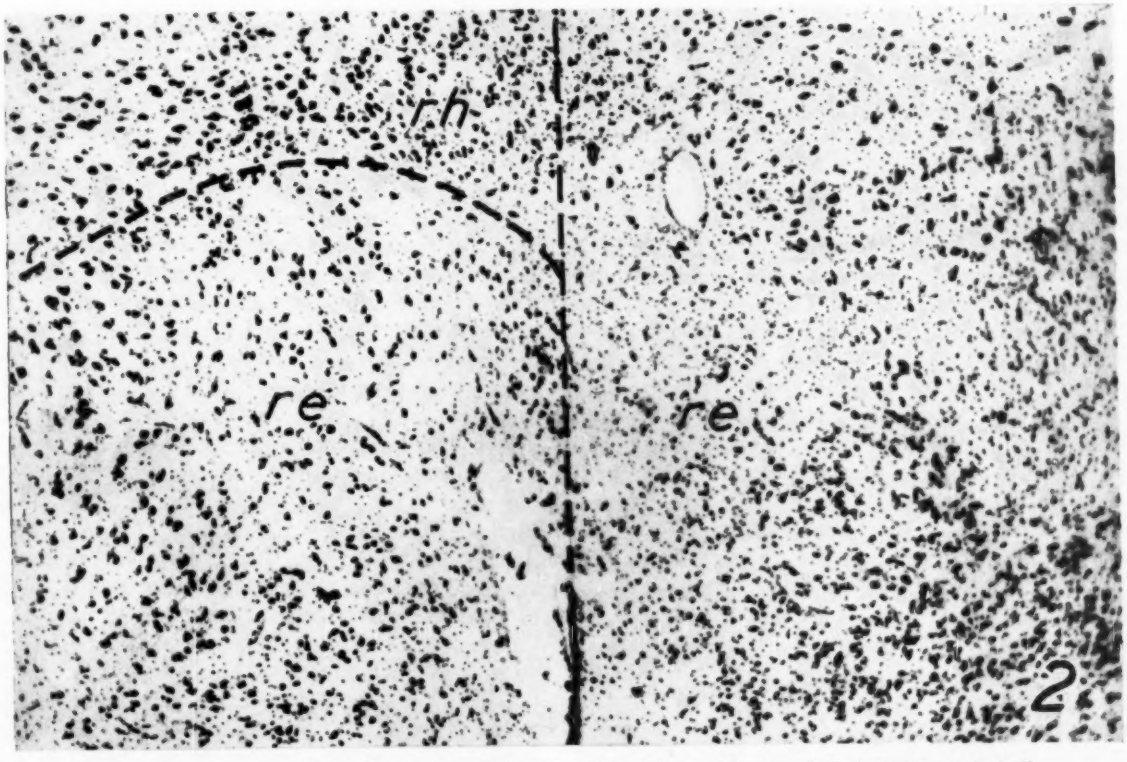
nuclei; it also indicates the pathway of their projection fibres.

Of the second group of experiments only Rabbits 15 and 60 will be described. In Rabbit 15 the lesion was confined to structures abutting on the medial surface of the hemisphere as far ventrally as the olfactory tubercle. In front of the level of the septum the caudate nucleus, the ventral half of the internal capsule, the putamen, and the nucleus accumbens have been completely destroyed; the rostral two-thirds of the septum of this side have also been ablated, but posteriorly the damage to the striatum becomes restricted to the medial half of the caudate nucleus and at the level of the posterior third of the septum it is minimal. The main portion of the lesion then extends back into the lateral preoptic area and the lateral half of the medial preoptic area destroying the anterior commissure and the ventro-medial quarter of the internal capsule at this level. The striatum (putamen and caudate nucleus) adjacent to the damaged internal capsule has suffered only marginal involvement. The lesion stops abruptly at the level of the anterior margin of the optic chiasma, the hypothalamus being unaffected.

In the thalamus the degeneration is limited largely to the nuclei of the midline and the internal medullary lamina. The nuclei reuniens, rhomboideus, centralis medialis, paracentralis, centralis lateralis and the parataenial show a marked cell loss throughout their antero-posterior extent. In the parafascicular nucleus there is a moderate degree of cell loss in its antero-medial part, but the rest of the nucleus is unchanged. The ventral vertical parts of the anterior and posterior paraventricular nuclei are also severely degenerate. Slight cell loss and cell shrinkage are seen in the medial thirds of the nucleus ventralis anterior and the reticular nucleus, accompanied by an intense gliosis which extends into the inferior thalamic radiation. Of the other principal nuclei, only the antero-medial, medio-dorsal, ventro-medial nuclei and the medial halves of the antero-dorsal, antero-ventral, ventro-basal and ventro-lateral nuclei show any retrograde cell degeneration. The thalamic degeneration in this experiment is obviously the result of the interruption of fibres in the internal capsule, again confirming our previous observation (Powell and Cowan, 1954) that the efferent fibres of these nuclei traverse the lower medial portion of the internal capsule.

In Rabbit 60 a well circumscribed electrolytic lesion was placed in the rostral part of the hemisphere destroying most of the head of the caudate





The sections were stained with either methylene blue or thionine. The magnification of all photomicrographs is 62.

PLATE 1.--Photomicrograph showing retrograde cell degeneration in the parataenial, ventral part of the paraventricular, interantero-dorsal, and antero-medial nuclei in experiment R 2.

PLATE 2.—Degeneration in the nuclei reuniens and rhomboideus in experiment R 54.

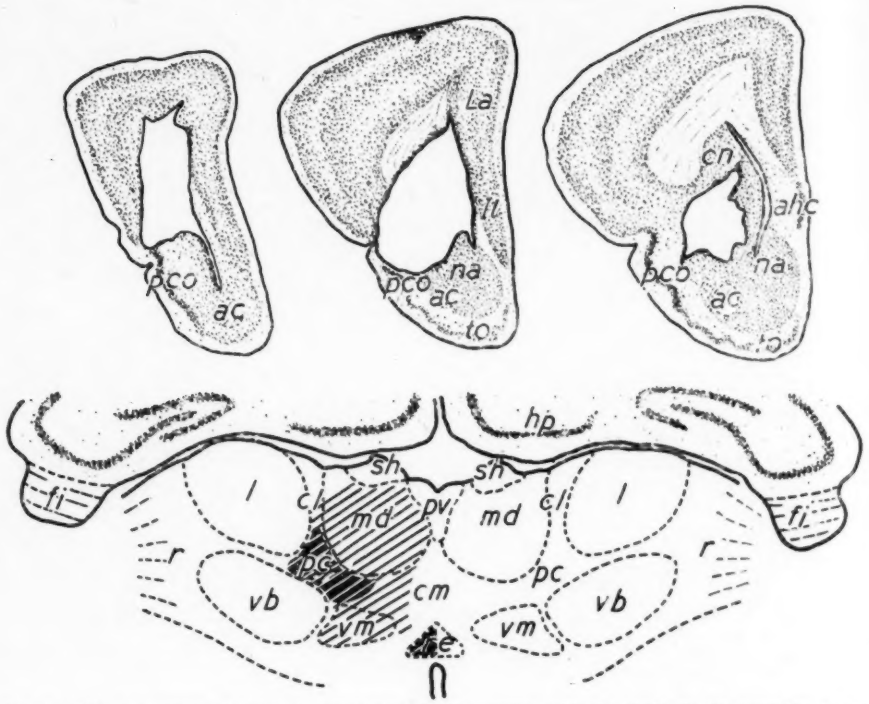
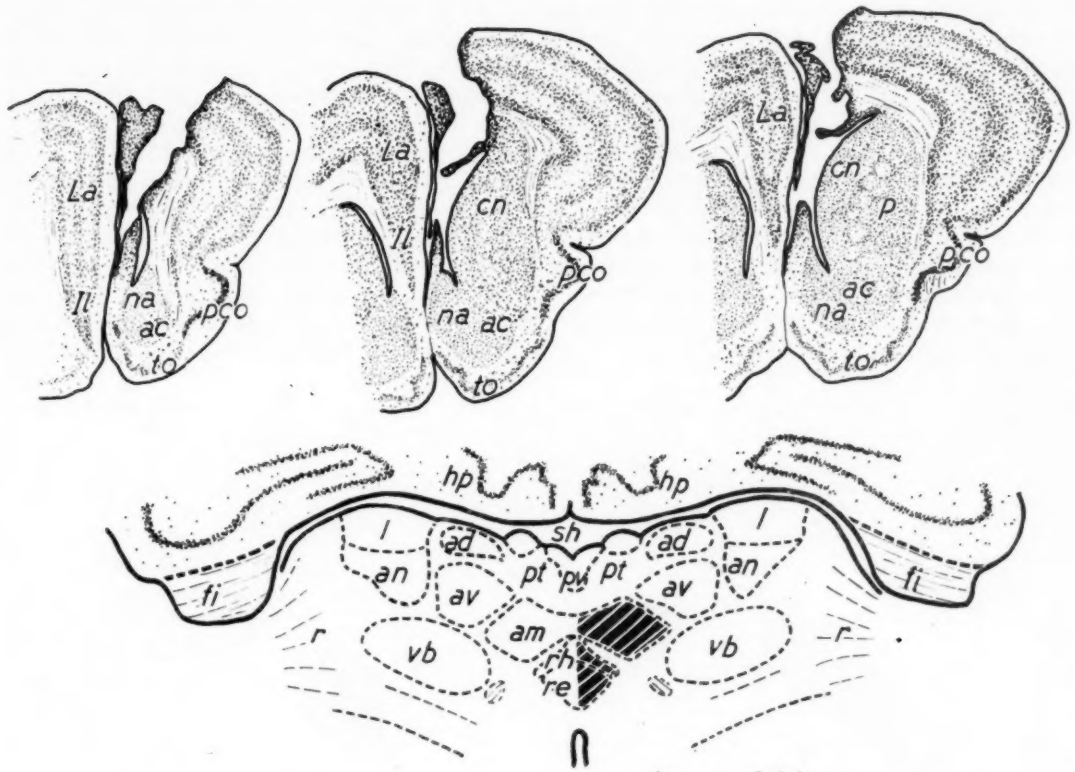

pco = pyriform cortex
ac = anterior commissure
to = olfactory tubercle
La = anterior limbic area
Il = infralimbic area
na = nucleus accumbens
cn = caudate nucleus
ahc = anterior hippocampal cortex
fi = fimbria
l = lateral nucleus
vb = ventro-basal nucleus
sh = stria habenularis
md = medio-dorsal nucleus
pc = nucleus paracentralis
vm = ventro-medial nucleus
r = reticular nucleus
pv = paraventricular nuclei
cl = nucleus centralis lateralis
cm = nucleus centralis medialis
re = nucleus reuniens
hp = hippocampus

FIG. 3.—Site and extent of lesion in experiment R 60 together with the thalamic degeneration in this experiment. There is almost total degeneration in nn. paracentralis and reuniens while there is severe cell loss in nn. centralis lateralis, medio-dorsalis, and ventro-medialis.

nucleus and the adjacent centrum ovale. In its antero-posterior length the lesion extends from the level of fusion of the anterior olfactory nucleus with the overlying neocortex back to just behind the genu of the corpus callosum. Rostral to the genu the head of the caudate nucleus, the putamen, and the dorsal margin of the nucleus accumbens have been completely destroyed. Immediately behind this level the lesion is restricted to the lateral part of the caudate nucleus and the adjacent middle portion of the internal capsule (Fig. 3). The resulting retrograde cell degeneration is found mainly in the midline and intralaminar group of thalamic nuclei (Fig. 3). The nucleus reuniens and the rhomboid nucleus have undergone severe cell loss, the remaining cells being shrunken and pyknotic. The nucleus centralis medialis shows a partial cell loss which is most severe in its lateral half where it adjoins the almost totally degenerate paracentral nucleus. The nucleus centralis lateralis is likewise severely degenerate in its medial half, but laterally there is no change apart from a slight gliosis. In the rostral part of the parafascicular nucleus where it adjoins the medio-dorsal nucleus there are slight changes in the form of shrinkage and compacting of the cells, together with a moderate degree of gliosis. The remaining midline nuclei (the parataenial and the anterior and posterior paraventricular) show no change. Shrinking and compacting of the constituent cells together with severe gliosis are present in the adjoining medial portions of the nucleus ventralis anterior and the reticular nucleus. The other principal nuclei which show changes are the antero-medial, dorso-medial, and ventro-medial, in all of which there is a severe diffuse cell loss and gliosis. The course of the degenerated fibres is indicated by a band of dense gliosis in the ventral third of the internal capsule.

In the subsequent two groups of experiments an attempt was made to determine to what extent the cortical and subcortical structures, which were damaged in the previous experiments, are implicated in the projection of the midline and intralaminar nuclei. In the first of these groups the lesions were strictly limited to the cortex on the medial surface of the hemisphere involving principally the anterior limbic and infralimbic areas. Some of these lesions were placed primarily for a study of the relationships between the cingulate cortex and the mamillary nuclei (Cowan and Powell, 1954), and as the projection of the anterior nuclei of the thalamus to the different areas of this cortex has already been established by Rose and Woolsey (1948) the degeneration in these nuclei will not be described in detail.



L a	=	anterior limbic area
l l	=	infralimbic area
n a	=	nucleus accumbens
a c	=	anterior commissure
t o	=	olfactory tubercle
p c o	=	pyriform cortex
c n	=	caudate nucleus
p	=	putamen

f i	=	fimbria
l	=	lateral nucleus
a n	=	angular nucleus
r	=	reticular nucleus
v b	=	ventro-basal nucleus
h p	=	hippocampus
a d	=	antero-dorsal nucleus
a v	=	antero-ventral nucleus
a m	=	antero-medial nucleus
p t	=	parataenial nucleus
p v	=	paraventricular nuclei
r h	=	nucleus rhomboideus
r e	=	nucleus reuniens

FIG. 4.—Extent of the lesion and the resulting thalamic degeneration in experiment R 54.

In Rabbit 54 the entire neocortex of the medial surface of the hemisphere was ablated from the posterior margin of the orbito-frontal cortex back to the genu of the corpus callosum. The serial sections show that the whole of the anterior limbic and infralimbic areas and the prefrontal agranular cortex on the medial surface have been destroyed together with the rostral part of the lateral septal nucleus. It should be emphasized, however, that at no point does the lesion encroach on the nucleus accumbens or the caudate nucleus (Fig. 4).

The retrograde cell degeneration in this experiment is confined to the nuclei reuniens and the rhomboideus of the midline group while the only principal nuclei which show cell loss are the antero-medial and the medial third of the ventro-lateral (Plate 2). The absence of degeneration in the parataenial nucleus and in the intralaminar group should be particularly noted (Fig. 4).

The extent of the cortical damage in four similar experiments of this group is shown in Fig. 5. In the thalamus of these hemispheres cell loss has occurred in the midline nuclei reuniens and rhomboideus and also in the various elements of the anterior and ventral principal nuclei.

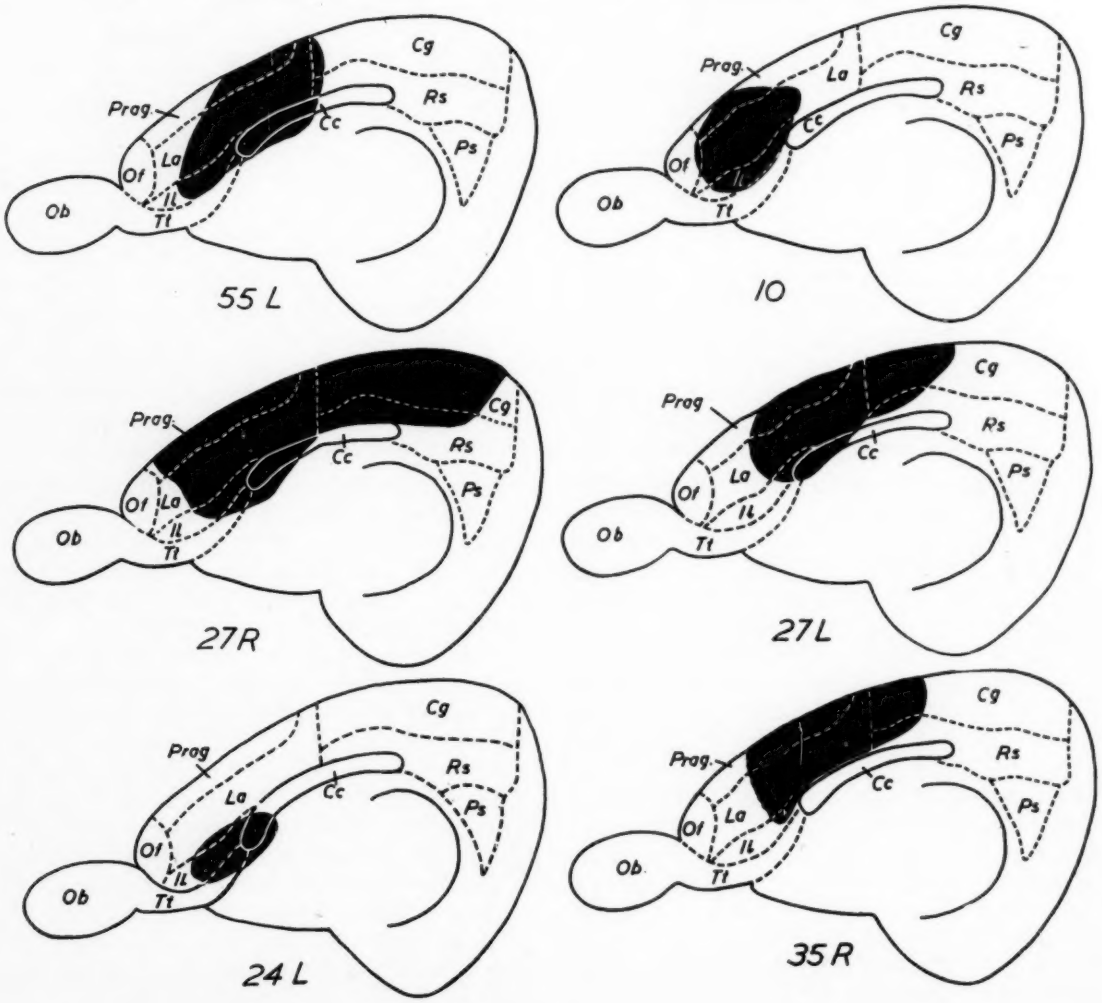
The cortical damage in experiment R 35R is mainly in the anterior limbic area, but in addition the postero-dorsal margin of the infralimbic field just above and in front of the genu of the corpus callosum and the precentral agranular areas are involved (Fig. 5). The fibres to the posterior cingulate and retro-splenial areas have also been interrupted. Of the midline thalamic nuclei, degeneration is found only in the nucleus reuniens in which slight cell loss is present throughout most of the cross-sectional area but is more marked in the dorsal third ; similar changes are found in the three anterior nuclei and the ventral nuclei.

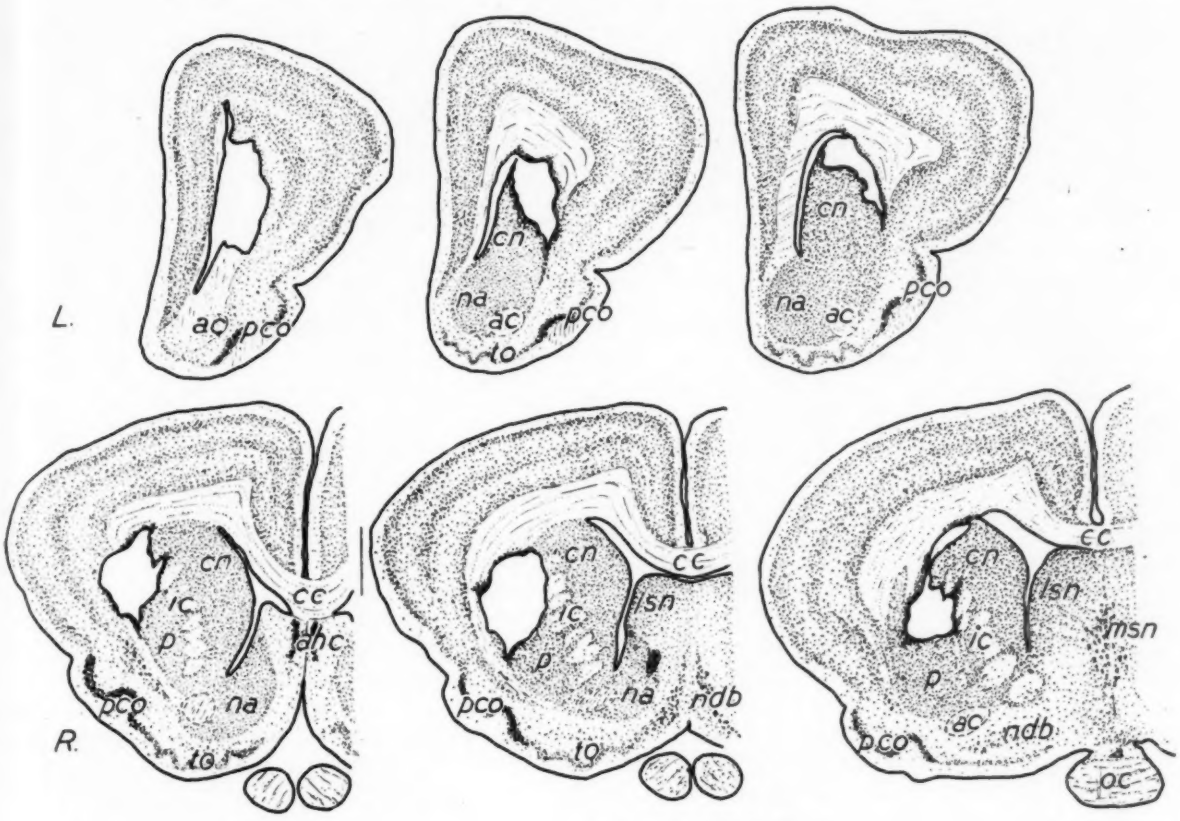
In all of the above experiments the anterior nuclei have degenerated in addition to the nucleus reuniens and the rhomboid nucleus. That the latter two have an independent projection, however, is shown in R 24L, in which the cortical damage is confined to the posterior two-thirds of the infralimbic area (Fig. 5) with a marginal involvement of the nucleus accumbens and the lateral septal nucleus. There is a diffuse cell loss throughout the antero-posterior extent of the nucleus reuniens and slight cell loss in the rhomboid nucleus. On the other hand there is no change in any of the anterior nuclei or the medio-dorsal nucleus.

In R 55R the caudate nucleus and the nucleus accumbens have been slightly involved in addition to most of the cortex on the medial surface. At the rostral end of the striatum there is a narrow knife cut into the dorso-lateral margin of the nucleus accumbens and this extends back to involve the medial and ventral parts of the caudate nucleus and the adjacent ventralmost part of the internal capsule. The only difference in the distribution of the thalamic degeneration in this hemisphere as compared with the experiments of the previous group is the diffuse cell loss throughout the entire antero-posterior extent of the parataenial nucleus.

FIG. 5.—The extent of the cortical lesions in experiments R 55L, R 10, R 27 (R and L), R 24L, and R 35R (sub-divisions of limbic cortex after Rose and Woolsey, 1948).

Prag	=	precentral agranular cortex	Tt	=	taenia tecta
La	=	anterior limbic area	Cg	=	cingulate area (posterior cingulate cortex)
Of	=	orbito-frontal cortex	Rs	=	retro-splenial area
Ob	=	olfactory bulb	Cc	=	corpus callosum
Il	=	infralimbic area	Ps	=	presubiculum





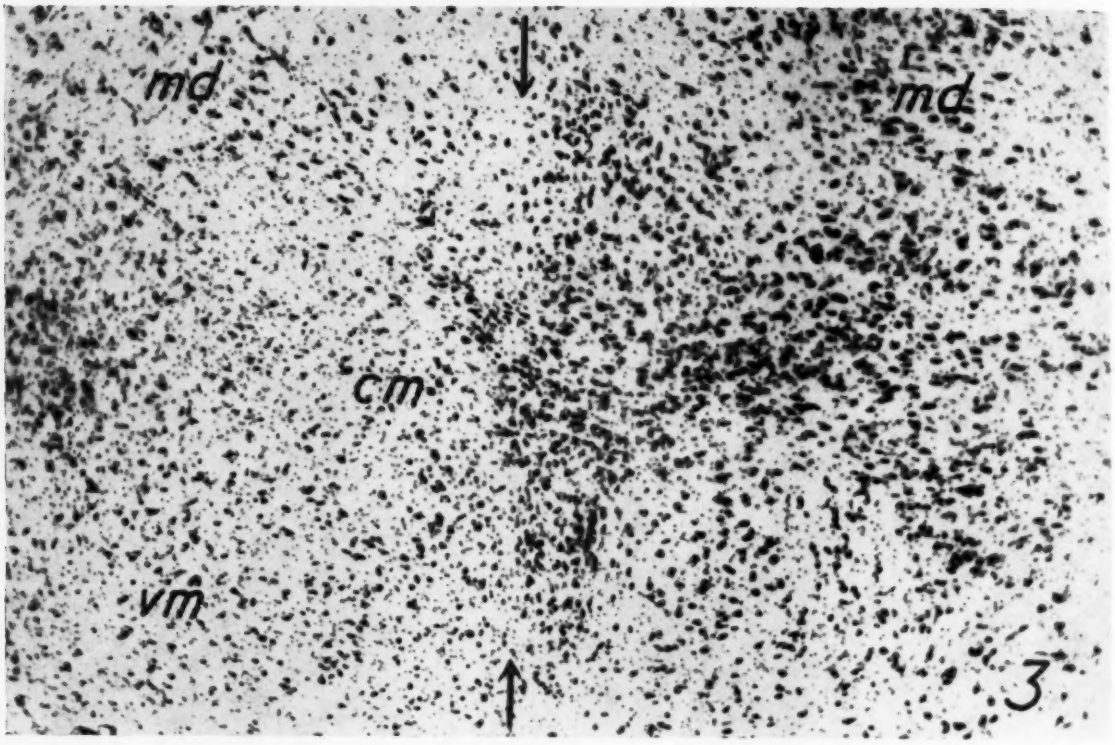
a c = anterior commissure
p c o = pyriform cortex
c n = caudate nucleus
n a = nucleus accumbens
t o = olfactory tubercle

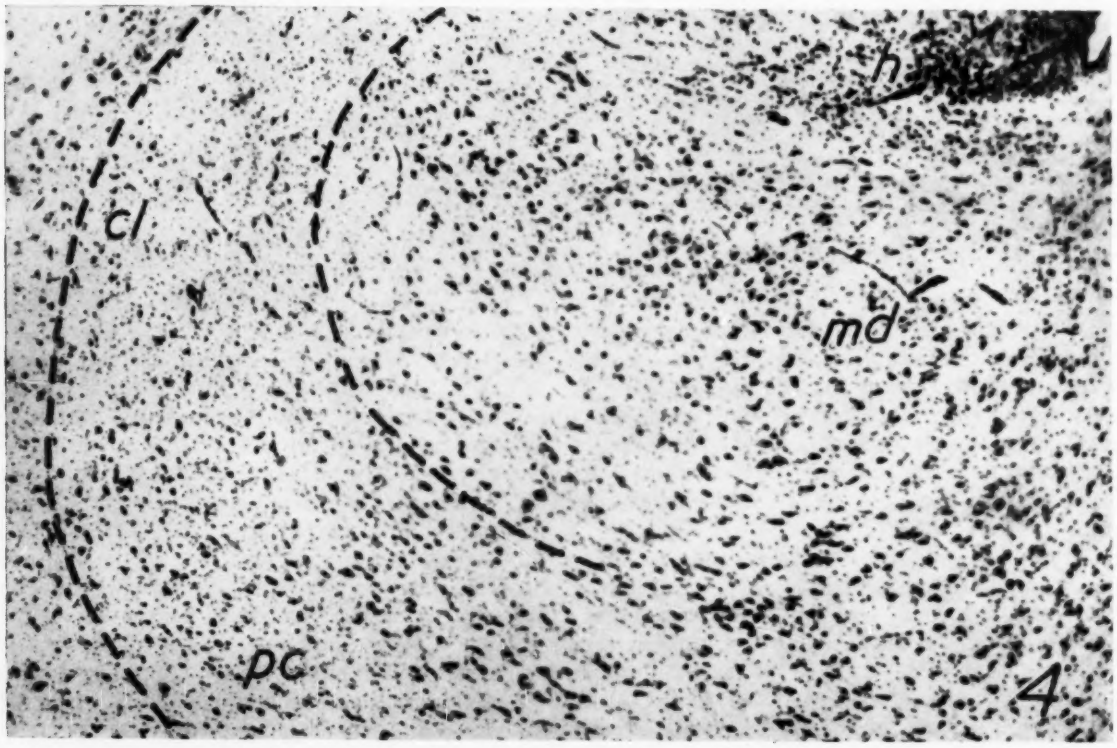
i c = internal capsule
p = putamen
C c = corpus callosum
a h c = anterior hippocampal cortex
l s n = lateral septal nucleus
n d b = nucleus of diagonal band
m s n = medial septal nucleus
o c = optic chiasma

FIG. 6.—Site of the lesion in experiment R 251R and L.

It can be concluded from these experiments that only certain of the midline nuclei, viz., the nucleus reuniens and the rhomboid nucleus, project directly to the cortex on the medial surface of the hemisphere. That the intralaminar nuclei likewise have a precise topical projection to the head of the striatum is demonstrated by the experiments of the following group.

In Rabbit 44 an electrolytic lesion was placed in the dorso-medial quadrant of the cerebral hemisphere extending from immediately in front of the anterior horn of the lateral ventricle back to the ventral hippocampal commissure. It either directly involves or isolates a large part of the anterior limbic, cingulate, and precentral agranular areas. The caudate nucleus is damaged from its anterior end back to the level of the middle of the septum; anteriorly the dorsal half of the nucleus is involved but the extent of the damage gradually diminishes posteriorly until it is limited to the dorso-medial ventricular margin. The dorsal part of the lateral septal nucleus is destroyed throughout its antero-posterior extent. In the thalamus the most significant cellular degeneration is in the nucleus centralis lateralis and the adjacent part of the nucleus paracentralis; in these areas almost complete cell loss has occurred and the few remaining cells are shrunken and pyknotic (Plate 4). The nucleus centralis medialis shows shrinkage and pallor of the cells in its lateral part only, while the parafascicular, parataenial, and paraventricular nuclei show no change. The rhomboid nucleus and nucleus reuniens are severely degenerated. In the nucleus ventralis anterior and the rostral portion of the reticular nucleus there is a wedge-shaped area of cell loss and gliosis immediately ventral to the degenerate antero-medial and medial half of the antero-ventral nuclei. The other main nuclei

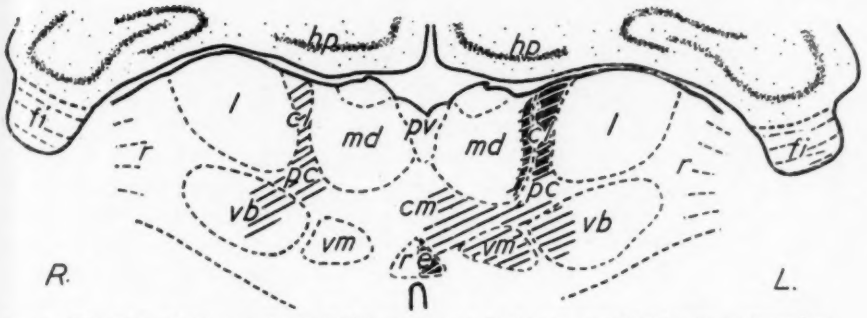




The sections were stained with either methylene blue or thionine. The magnification of all photomicrographs is 62

PLATE 3.—Degeneration in the nucleus centralis medialis and the adjacent medio-dorsal and ventro-medial nuclei in experiment R 251L.

PLATE 4.—Degeneration in the nuclei centralis lateralis, paracentralis, and the adjacent part of the medio-dorsal nucleus in experiment R 44.



fi = fimbria
r = reticular nucleus
l = lateral nucleus
v b = ventro-basal nucleus
h p = hippocampus
c l = nucleus centralis lateralis
p c = nucleus paracentralis
vm = ventro-medial nucleus
p v = paraventricular nuclei
c m = nucleus centralis medialis
r e = nucleus reuniens

FIG. 7.—The thalamic degeneration in R 251, most severe in the nn. centralis lateralis and reuniens of the right side.

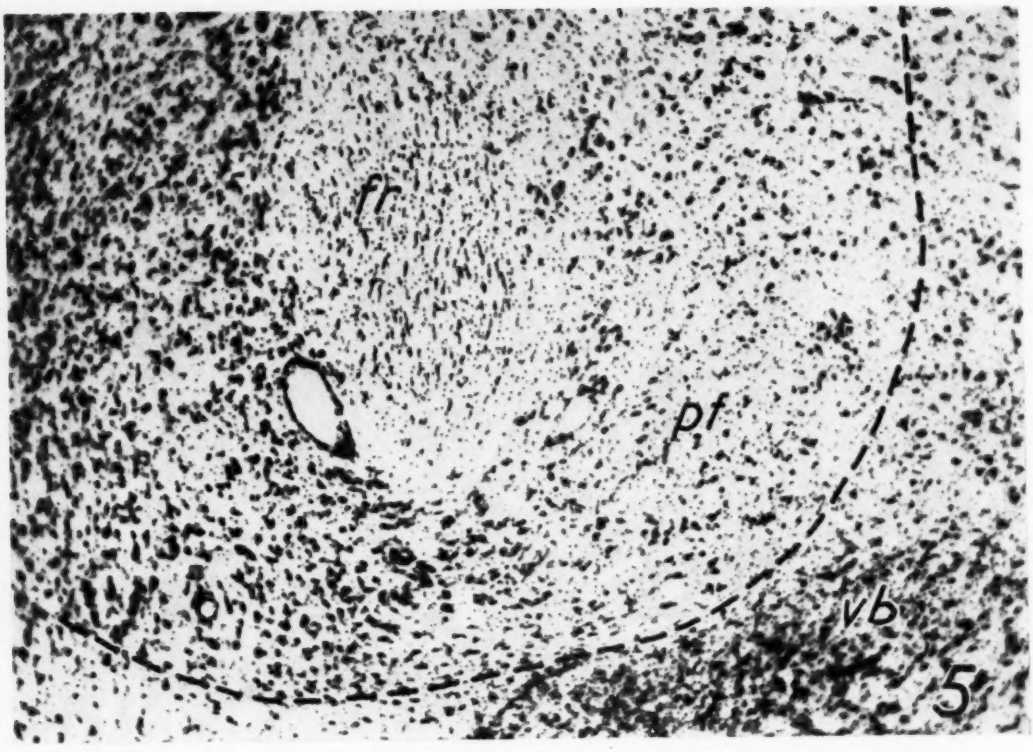
which show degeneration are the lateral part of the medio-dorsal (close to the degenerated nucleus centralis lateralis), the ventro-medial, and the medial parts of ventro-lateral and ventro-basal nuclei.

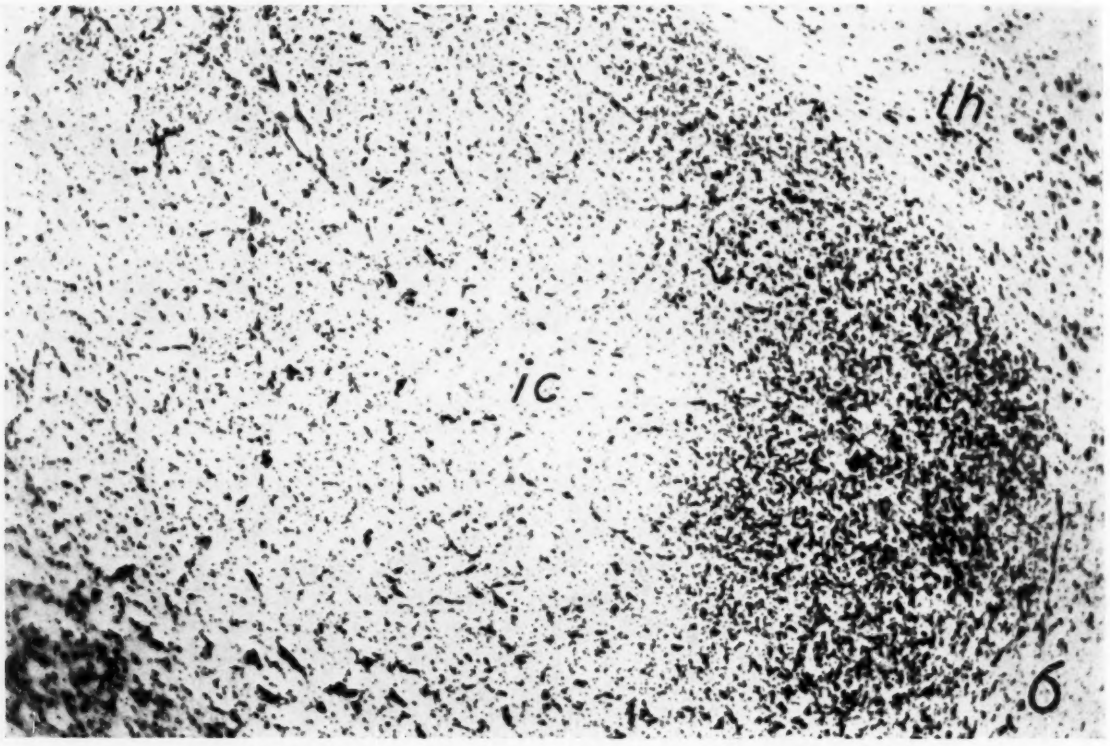
In R 251L there is a sharply circumscribed electrolytic lesion in the dorsal one-third to one-half of the head of the caudate nucleus with only minimal involvement of the immediately adjacent cortex and subcortical white matter ; the damage does not extend behind the level of the genu of the corpus callosum (Fig. 6). The nuclei reuniens and rhomboideus are severely degenerate; in the nucleus centralis medialis there is a marked cell loss while the remaining cells are shrunken and compacted together and the nucleus paracentralis shows a slight diminution in the number of cells and many of the persisting cells are poorly stained (Plate 3). The nucleus centralis lateralis is almost completely atrophied with an accompanying severe gliosis ; this degeneration is directly continuous with a similar small area in the lateral part of the medio-dorsal nucleus. The parataenial, parafascicular, and paraventricular nuclei show no change. The rostral end of the reticular nucleus and the overlying nucleus ventralis anterior show slight cell loss as well as compacting of the remaining cells beneath the partially degenerated antero-medial nucleus. The medial thirds of the ventro-lateral and ventro-basal nuclei together with the ventro-medial nucleus have undergone partial degeneration (Fig. 7).

In the opposite hemisphere of R 251 a lesion was placed in the dorsal half of the putamen from the level of the genu of the corpus callosum back to the level of crossing of the anterior commissure. Laterally the claustrum and the overlying neocortex have been involved while a narrow medial extension of the lesion crosses the upper end of the internal capsule to encroach upon the dorso-lateral margin of the head of the caudate nucleus (Fig. 6). In the thalamus of this side the cell degeneration is almost confined to the intralaminar nuclei and the only changes in the main nuclei are found in the medial part of the antero-ventral nucleus and in the middle thirds of the ventro-basal and ventro-lateral nuclei, all of which are partially degenerated. In the middle thirds of their medio-lateral extent the nucleus ventralis anterior and the adjoining reticular nucleus show slight cell loss and gliosis. Partial cell loss and gliosis have occurred in the nucleus centralis lateralis without any apparent change in the medio-dorsal nucleus while in the nucleus paracentralis there is a diffuse thinning out of the cells. There is a severe cell loss in the ventral half of the parafascicular nucleus, particularly in its posterior part in which the portion of the nucleus lateral to the habenulo-peduncular tract is almost completely atrophied (Plate 5). All the midline nuclei (parataenial, paraventricular, rhomboid, and reuniens) and the n. centralis medialis are unchanged (Fig. 7).

That the projection fibres of the midline and intralaminar nuclei neither terminate in nor traverse the medial preoptic area is indicated in experiment Rabbit 45. In this animal there is a well localized lesion in the medial preoptic area and the anterior hypothalamus. The electrode had been passed in a slightly caudal direction through the hemisphere close to the midline starting at the level of the anterior commissure ; the posterior two-thirds of this commissure is destroyed together with the dorsal third of the medial preoptic area as far laterally as the bed nucleus of the stria terminalis. Caudally the lesion reaches as far back as the paraventricular hypothalamic nucleus destroying the descending column of the fornix. Near its caudal limit the upper margin of the lesion abuts on the thalamic reticular nucleus while laterally it adjoins (but does not involve) the inferior thalamic radiation. There is no retrograde degeneration in any of the thalamic nuclei as a result of this lesion ; the absence of degeneration in the anterior paraventricular nucleus in particular should be noted.

The complete lack of degeneration in the midline and intralaminar nuclei in the thalamus of the left





The sections were stained with either methylene blue or thionine. The magnification of all photomicrographs is 62.

PLATE 5.—Degeneration in the lateral half of the parafascicular nucleus in experiment R 251R.

PLATE 6.—The severe gliosis in the ventral third of the internal capsule following a large lesion in the corpus striatum in experiment R 42.

hemisphere in Rabbit 35 excludes a projection from these nuclei to the septum. On this side the knife has entered the dorsal margin of the septum from the opposite limbic cortex at the level of the anterior end of the medial septal nucleus and extends back to the ventral hippocampal commissure. The entire medial septal nucleus, the posteromedial half of the lateral septal nucleus, and the vertical limb of the diagonal band nucleus have been directly damaged, while the rest of the lateral septal nucleus shows severe cell loss with shrinkage and compacting of the remaining cells.

The final experiments to be described demonstrate the pathway of the efferent fibres from the midline and intralaminar nuclei. In R 52 a lesion was placed in the middle third of the internal capsule extending forwards from the anterior end of the thalamus into the dorsal part of the striatum ; the most medial fibres of the internal capsule, however, have been spared. Although the midline nuclei, i.e., the reuniens, rhomboid, and parataenial, are unchanged, all the intralaminar nuclei, including the parafascicular, are totally degenerated, showing that there is a precise and independent pathway for these two groups of nuclei. Selective degeneration has occurred in the nucleus reuniens and rhomboid nucleus in R 57 following a small lesion in the most medial portion of the internal capsule at the level of the rostral end of the striatum, which is also damaged. This experiment when taken in conjunction with the earlier findings suggests that the fibres from these nuclei, after leaving the internal capsule, pass round the rostral end of the head of the caudate nucleus and the anterior limit of the lateral ventricle to reach the medial surface of the hemisphere. That this is indeed the case is seen in R 24R in which gliosis is present in the white matter medial to the anterior horn of the lateral ventricle well in front of the cortical lesion.

Discussion

The conclusion reached by Rose and Woolsey (1943) that the nuclei of the midline and internal medullary lamina are telencephalic dependencies has been fully substantiated by the experiments described in this and in our previous study (Powell and Cowan, 1954). However, with the exception of the recent work of Fortuyn (1950), and Stefens and Fortuyn (1953), no attempt has been made to define the projection of the individual elements of this system. An analysis of the material presented here in conjunction with earlier observations has to some extent clarified this problem.

That the nucleus reuniens and the rhomboid nucleus (as defined above) have a projection which is independent of the remainder of the midline and intralaminar nuclei has been clearly shown. In the experiments of the third group, these nuclei underwent complete selective, retrograde cell degeneration following lesions confined to the cortex on the medial surface of the hemisphere without any involvement of subcortical tissue. A correlation of the extent of cortical damage with the severity of degeneration in these experiments indicates that they project to the region of the infralimbic cortex (area 25 of Brodmann). This was conclusively established in the critical experiment R 24L in which the cortical damage was confined to the infralimbic area and the ensuing retrograde degeneration to the nucleus reuniens and the rhomboid nucleus. In their study of the connexions of the anterior nuclei in the rabbit and cat, Rose and Woolsey (1948) mention that in one experiment (RW18) severe degeneration was present in their "medio-ventral nucleus" (= nucleus reuniens) after a lesion confined largely to the infralimbic cortex and conclude from this and their other experiments, in which this region was incidentally involved, that this cortical area represents the projection field of the nucleus. A similar conclusion was reached by Fortuyn (1950) in his study of the paramedian and submedial nuclei.

The experiments of the third group also make it clear that no other midline thalamic nuclei project to the medial surface of the hemisphere or the septum. It has been suggested by some (Stoffels, 1939 ; Lashley, 1941 ; Fortuyn, 1950) that the parataenial nucleus may project to the most basal part of the medial surface of the hemisphere (retrobulbar area and taenia tecta), but this conclusion is not supported by our experiments. That the nucleus does project to the medial part of the rostral telencephalon is apparent from the consistent retrograde degeneration which occurs in the experiments with large lesions in this area (e.g., Rabbits 2 and 15). Degeneration was also seen in this nucleus in experiment R 55R in which the medial parts of the caudate nucleus and nucleus accumbens were damaged together with the cortex on the medial surface of the hemisphere. However, complete destruction of the head of the caudate nucleus with only marginal involvement of the nucleus accumbens (e.g., Rabbits 60 and 59) results in no marked retrograde change in the parataenial nucleus. From this it must be concluded that the parataenial nucleus is connected either with the nucleus accumbens or with the overlying olfactory tubercle. In our previous study (Powell and Cowan, 1954) a projection of the parataenial nucleus to the rostromedial two-thirds of the olfactory tubercle was

excluded by experiment R.12. This experiment has been re-examined and it has been confirmed that the lesion is strictly confined to this portion of the olfactory tubercle with little or no involvement of the nucleus accumbens and that there is no apparent change in the parataenial nucleus. It would thus appear that the efferent fibres of the parataenial nucleus terminate either in the nucleus accumbens or in the lateral part of the olfactory tubercle. In some of our experiments in which the nucleus accumbens was marginally involved there was often a suggestion of cell loss along the margins of the parataenial nucleus although no serious atrophy of the nucleus was apparent. Since we have no lesion which completely destroys the nucleus accumbens without involvement of other adjacent structures this point has not been conclusively determined. Our findings are not entirely at variance with the observations of the authors quoted above, as it is clear from the diagrams of their lesions that the nucleus accumbens or the adjacent internal capsule were usually involved (cf. Fortuyn, 1950). Furthermore, as Rose and Woolsey (1943) point out, Stoffels' (1939) suggestion that the taenia tecta is the projection area for this nucleus seems to have been an indirect conclusion only.

In our previous study (Powell and Cowan, 1954) degeneration of the anterior and posterior paraventricular nuclei was described in six experiments in some of which an extensive lesion of the basal forebrain areas extended back into the anterior hypothalamus; the only other description of degeneration in these nuclei is that of Walker (1936) in the monkey after a lesion in the medial preoptic and anterior hypothalamic areas. In the first two experiments described in the present communication, partial degeneration has occurred in these nuclei after large lesions of the striatum and basal forebrain areas but without involvement of the hypothalamus. Further, in one experiment (Rabbit 45) in which the lesion was confined to the medial preoptic and anterior hypothalamic areas no degeneration was seen in these nuclei. It thus appears that these nuclei will undergo degeneration following extrathalamic lesions but it has not been possible to determine their projection (cf. Rose and Woolsey, 1943). The nucleus centralis medialis, on the other hand, appears to project in close association with the intralaminar nuclei—paracentralis and centralis lateralis—to the caudate nucleus. In the majority of the experiments, in which the lesions were confined largely to the dorso-lateral part of the head of the caudate nucleus, the severity of the thalamic degeneration was most marked in the nucleus centralis lateralis and was usually least marked in the nucleus centralis medialis. Although it has not been possible to determine the precise termination of the efferent fibres of each of these elements, in experiments involving different parts of the head of the caudate nucleus the distribution and severity of the retrograde degeneration in these thalamic nuclei varied quite definitely, suggesting that each has an independent projection to the caudate. That the projection of these three intralaminar nuclei is also independent of the principal thalamic nuclei is apparent from those experiments in which they have undergone degeneration without any appreciable change in the adjacent main nuclei. This conclusion is in accord with the findings of Stefens and Fortuyn (1953), and it is now well established that there is a direct thalamo-caudate projection.

Although it has been frequently suggested that the parafascicular nucleus of lower mammals projects to the striatum (cf. Stefens and Fortuyn, 1953), the only experimental evidence which has been adduced to support this hypothesis is that of Gerebtzoff (1940). The experiments described in our paper indicate quite clearly that the parafascicular nucleus projects to the putamen, and, if the lateral part of this nucleus is indeed homologous with the centre median of primates (Le Gros Clark, 1931), it too would have a similar projection. This is in accord with the reports of degeneration in the centre median in human pathological material with lesions involving the striatum (Vogt and Vogt, 1941; McLardy, 1948).

Our findings on the degeneration in the reticular nucleus are similar to those previously described (Rose, 1952; Chow, 1952; Powell and Cowan, 1954). The nucleus ventralis anterior, which has recently been shown to be an important element in the diffuse projection system of the thalamus (Starzl and Magoun, 1951; Hanbery and Jasper, 1953), frequently showed marked degenerative changes in these experiments. These findings will, however, not be discussed here as the efferent connexions of this nucleus are being further investigated.

From the variety of lesions which have been placed, and by tracing out the ensuing gliosis, it has been possible to determine the precise pathway of the efferents from the midline and intralaminar nuclei to the striatum and the infralimbic area. The fibres leave the thalamus in the inferior thalamic radiation, pass forwards in the ventral third of the internal capsule, the fibres from the parafascicular nucleus diverging laterally into the putamen while the remainder continue forwards towards the head of the caudate nucleus. Here the fibres from the

nucleus reuniens, the rhomboid, and the parataenial nuclei occupy the most ventral part of the internal capsule, while the intralaminar projection fibres which lie more dorsally swing medially into the caudate nucleus. The fibres to the infralimbic cortex then course around the rostral end of the caudate nucleus before terminating in the medial surface of the hemisphere.

The observations reported herein provide an anatomical basis for the physiological work of Stoupel and Terzuolo (1954) and Shimamoto and Verzeano (1954) on the relation of the caudate nucleus to the diffuse thalamic projection system.

Summary

The efferent connexions of the midline and intralaminar nuclei of the thalamus have been investigated in the rabbit by the method of retrograde cell degeneration.

It has been established that these nuclei have extrathalamic connexions; with the exception of the paraventricular nuclei, they project by way of the inferior thalamic radiation to the corpus striatum and the adjacent cortex of the medial surface of the hemisphere.

The intralaminar nuclei, centralis medialis, paracentralis, and centralis lateralis, project to the head of the caudate nucleus while the parafascicular nucleus is connected with the putamen.

The midline nuclei reuniens and rhomboideus project directly to the cortex of the infralimbic area.

The precise connexions of the cells of the paraventricular and parataenial nuclei could not be determined but the latter is probably connected with the nucleus accumbens.

We wish to thank Mr. Michael Lindsey and Mr. Brian Purvis for valuable technical assistance.

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NON-SPECIFIC EFFECTS OF INSULIN AND ELECTROPLEXY

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The recognition of the non-specific action of chemical or other agents used therapeutically owes much to the theories and experimental work of Selye (1950a). He traced out a pattern of reaction which longitudinally was termed the general adaptation syndrome (Selye, 1946) and in cross-section appears to be essentially triphasic (Selye, 1950b). Selye suggested that the first part of this be known as the alarm reaction, the implication being that adaptation had not as yet been acquired ; this was followed by the stage of resistance during which adaptation was optimal, and if the stimulus or stress should persist, then the stage of exhaustion supervened. An agent producing an alarm reaction was termed a stressor (Selye, 1950c) and might exert both specific and non-specific effects (Selye, 1951). Insulin, for instance, acts both non-specifically (Paschkis, Cantarow, Walkling, and Boyle, 1950) and specifically by increasing the peripheral assimilation of sugar and the deposition of glycogen in the liver (Soskin, 1941 ; Bouckaert and de Duve, 1947).

The value of both insulin and electroplexy (E.C.T.) in the treatment of the schizophrenias has been thought of by some to owe much to their non-specific effects. Thus Roth and Rosie (1953) liken the action of E.C.T. to that of other non-specific therapies such as A.C.T.H. and cortisone, emphasizing that it is unlikely to act directly upon the causes of psychiatric disorders but rather upon the regulatory and defensive mechanisms of the organism. Sackler, Sackler, Sackler, La Burt, van Ophuijsen, and Co Tui (1951), while admitting a number of physiological denominators common to E.C.T., insulin coma therapy, histamine and combined sex hormone therapies, nevertheless considered that to explain away all their effects as being non-specific might amount to the dismissal of other important factors in their action.

It is the purpose of this paper to suggest that various biochemical and tissue deviations that have been hitherto assigned either diagnostic or prognostic status, and which occur concurrently with, and in apparent direct relation to, treatment could as reasonably be integrated with patterns of non-specific homeostasis.

Such criteria include that of Meduna (1950), who postulated a clinical distinction between endogenous schizophrenia and a syndrome he designated "oneirophrenia", one of the differences being that the latter patients exhibited resistance to insulin in the intravenous insulin tolerance test. This resistance was a reversible phenomenon, the reaction reverting to a normal hypoglycaemic response *pari passu* as the patient improved with the administration of E.C.T., the reversion being an additional hall-mark of the benignity of the condition in contrast to the more sinister outlook for the true schizophrenias.

Other work on prognostic criteria includes that of Rud (1947a) who demonstrated that the administration of "cardiazol", E.C.T., and deep insulin therapy was succeeded by an immediate eosinopenia, but that in addition three weeks after beginning insulin there was a distinct increase in the eosinophil cells. He deemed that this rising eosinophil count was of therapeutic importance and that it indicated a patient who might benefit from one of the shock treatments. Sackler and others (1951) also observed an apparent correlation between an improvement in the patient's clinical status and the degree of eosinophilia. Altschule, Siegel, Restaino, and Parkhurst (1952) remarked upon this eosinophilia in patients who showed improvements after shock treatments, and affirmed that in their study patients with decreases in the cell count persisting after the end of treatment were not improved. Similarly, Alexander and Neander (1953) comment that in their series those patients who showed no rise in the resting eosinophil count during therapy evinced no alteration in their eventual mental state. Shands and Menzer (1953) dissent from these opinions, suggesting that the evidence of prognostic significance for the occurrence, or non-occurrence, of eosinophilia in relation to treatment was not convincing.

* Abstracted partly from a thesis accepted for the degree of M.D. Cantab., 1953.

Therefore, in an attempt to elucidate the matter further, a series of sequential investigations, including repeated insulin tolerance tests, eosinophil counts, and plasma chloride values, was recorded on patients treated with E.C.T. and with both deep or modified insulin.

Methods

The technique adopted for the insulin tolerance test was that proposed by Fraser, Albright, and Smith (1941) who recommend the intravenous administration of 0·1 unit of insulin per kg. of ideal body weight. As the previous diet influences the response to insulin (Himsworth, 1935) the patients were given at least 300 g. carbohydrate daily for three days before the test. All patients came to the ward at 7.30 a.m. and remained at rest in bed until the test began at approximately 9 a.m. when they had then been fasting for 12 hours. Blood was first removed for the initial eosinophil count, as it is known that following the eosinopenia during the early hours of the morning the count tends to become stabilized about 9 a.m. with a minimum between 9 a.m. and 11 a.m. (Rud, 1947b). Capillary blood was then withdrawn for estimation of the fasting blood sugar, after which the insulin was injected. At 20, 30, 45, 60, 90, and 120 minutes afterwards further samples of blood were taken. The blood sugars were estimated by the method devised by Herbert and Bourne (1930), which is a determination of the true blood glucose. As it has been demonstrated that hypoglycaemia is accompanied by an eosinopenia (Perlmutter and Mufson, 1951) and that this is most prominent four hours after stress, the eosinophils in addition to being counted at 9 a.m. were also checked at 1 p.m. The difference between the 9 a.m. and 1 p.m. counts for the group was calculated and termed the " mean eosinopenia."

As the results of insulin tolerance tests repeated at short intervals were being compared, it was essential to show that repeated tests under normal circumstances manifested no significant statistical dissimilarity. This was done and it was seen that the results of insulin tolerance tests repeated at short intervals were strictly comparable (Marley, 1953). Patients were therefore tested before treatment, during the fifth to twelfth days of treatment, between the thirteenth day and the end of treatment, and within 10 days of the termination of therapy. In the case of those tests performed during the course of treatment, patients were rested from the latter for three days before testing, not only to ensure that the strictures as regards diet were observed but also to exclude any immediately preceding effect of recent therapy. The criterion of a fall of less than 50% of the fasting blood sugar, or a fall not occurring for 45 minutes or more, was adopted as being indicative of insulin resistance (Fraser and others, 1941). In addition, the mean fall of blood sugar 30 minutes after the beginning of the test was calculated for the group as a whole and compared before, during, and after cessation of treatment.

Capillary blood was used in eosinophil counting, and both the technique and the phloxine-urea diluent proposed by Manners (1951) were adopted. The eosinophil counts performed during treatment, but not associated with insulin tolerance tests, were also done at approximately 9 a.m., and those reported here derive from the mean of two counts estimated twice weekly.

For each count, two white-cell pipettes were filled to the 1 mark with blood and to the 11 mark with the phloxine-urea diluent. The pipettes were immediately shaken for two to three minutes and then the four counting chambers (two double-sided Fuchs-Rosenthal chambers) were filled by capillation. The counting chambers were set aside in a moist environment prepared by placing a few sheets of filter paper soaked with water in the bottom of a large Petri dish. Within 15 minutes nearly all the leucocytes other than the eosinophils were lysed. The count was then performed under the 16 mm. microscope objective with a $\times$ 10 eyepiece. All the ruled area of the chamber was counted, and as the total volume of the four chambers was 12·8 c.mm. and the dilution 1 in 10, the number of eosinophils per c.mm. was ascertained by dividing the total number counted by 1·28.

Plasma chloride values were estimated by first precipitating silver chloride with the addition of a known amount of silver nitrate and then destroying the proteins by heating with nitric acid. The remaining silver nitrate was titrated with thiocyanate and the amount precipitated calculated, and hence the amount of chloride determined (May and Marrack, 1951).

No patient was accepted for testing if he was markedly underweight, as it has been demonstrated that changes attributable to the general adaptation syndrome are constantly present in association with severe malnutrition (Selye, 1950d). For the same reason patients treated in the previous two months with either E.C.T. or deep or modified insulin were rejected (Gellhorn and Safford, 1948 ; Henneman, Altschule, and Siegel, 1951).

The results of investigations performed on 22 psychotic patients treated with deep insulin (Nos. 1 to 22), five psychotics treated with E.C.T. (Nos. 23 to 27), and seven patients suffering from neurotic illnesses treated with modified insulin (Nos. 28 to 34) were analysed and compared statistically.

All the values included below derive from tests on the entire groups of patients except for the eosinophilias associated with deep insulin treatment which were calculated from repeated counts on 16 of the 22 psychotics, and the plasma chloride readings which were obtained from repeated estimations on seven of the 22 psychotics of that same group.

The patients were all males, those suffering from psychoses being diagnosed as having schizophrenia. In no instance was an alternative diagnosis of oneirophrenia tenable.

Results

The mean values and their standard deviations derived from the results of tests are presented in Tables I, II, and III. The mean fall of blood sugar, the mean eosinopenia, the mean fasting blood sugar levels, and the mean plasma chloride values were

TABLE I

MEAN AND STANDARD DEVIATION VALUES DERIVED FROM TESTS ON PATIENTS TREATED WITH DEEP INSULIN

Indices	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy
Fall of blood sugar (mg.)	40·8 ± 7·41	47·0 ± 9·63	45·3 ± 11·11	46·4 ± 8·12
Fall of blood sugar (%)	53·6 ± 6·44	57·9 ± 10·10	55·4 ± 12·21	57·3 ± 8·75
Fasting blood sugar (mg./100 ml.)	75·5 ± 8·67	81·4 ± 8·82	81·1 ± 9·87	81·2 ± 7·00
Eosinopenia (%)	79·6 ± 14·16	43·9 ± 20·32	25·4 ± 24·42	20·5 ± 30·20
Eosinophils (per c.mm.)	142·7 ± 67·17	208·7 ± 83·92	250·4 ± 129·27	134·4 ± 62·00
Plasma chlorides (mEq.)	92·0 ± 2·76	103·2 ± 10·10	93·5 ± 2·95	95·3 ± 7·39

TABLE II

MEAN AND STANDARD DEVIATION VALUES DERIVED FROM TESTS ON PATIENTS TREATED WITH E.C.T.

Indices	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy
Fall of blood sugar (mg.)	42·8 ± 7·05	49·2 ± 6·22	48·6 ± 5·18	42·0 ± 11·56
Fall of blood sugar (%)	58·4 ± 5·31	62·4 ± 7·54	59·6 ± 6·39	56·8 ± 9·09
Fasting blood sugar (mg./100 ml.)	72·8 ± 5·97	79·2 ± 4·32	81·6 ± 4·39	77·2 ± 4·21
Eosinopenia (%)	82·2 ± 11·44	45·2 ± 13·87	15·4 ± 12·29	13·0 ± 12·62
Eosinophils (per c.mm.)	21·4 ± 11·15	40·6 ± 30·95	125·2 ± 57·09	68·4 ± 39·02

TABLE III

MEAN AND STANDARD DEVIATION VALUES DERIVED FROM TESTS ON PATIENTS TREATED WITH MODIFIED INSULIN

Indices	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy
Fall of blood sugar (mg.)	40·7 ± 5·47	45·0 ± 5·49	46·2 ± 11·84	45·4 ± 19·67
Fall of blood sugar (%)	54·3 ± 4·77	57·1 ± 4·73	56·2 ± 10·27	54·8 ± 18·69
Fasting blood sugar (mg./100 ml.)	74·6 ± 5·25	78·6 ± 4·57	83·2 ± 4·53	80·5 ± 9·99
Eosinopenia (%)	70·4 ± 13·34	49·1 ± 26·73	28·0 ± 27·51	5·3 ± 82·75
Eosinophils (per c.mm.)	187·1 ± 118·16	205·0 ± 154·50	189·4 ± 110·79	96·8 ± 43·84

obtained at the same time as the insulin tolerance tests. The mean level of the eosinophils, as explained previously, was calculated from the mean of twice weekly counts performed before, during, and after therapy, although those included here are the means of the maximum eosinophilias recorded in that period. The mean fall of blood sugar represents the mean of the differences between the fasting blood sugars and the values 30 minutes after the beginning of the insulin tolerance test.

From these Tables it can be seen that the mean fall of blood sugar is increased during and immediately after the cessation of therapy, most particularly between the fifth and twelfth days of treatment. Similarly, the mean of the fasting blood sugars is increased during and immediately after therapy, most noticeably during the later phases of treatment. The mean eosinopenia declines rapidly during and immediately after therapy. The mean value for the plasma chlorides increased during treatment with deep insulin, most markedly between the fifth and twelfth days of therapy. The mean level of eosinophils increased during treatment, the greatest increase taking place during the earlier stages of the course of modified insulin but during the later phases of treatment with deep insulin or E.C.T. However, this mean increase had disappeared soon after the termination of therapy.

The significance of the differences between these mean values has been assessed statistically and presented in Tables IV, V, and VI. The means compared were those obtained before treatment and those found between the fifth and twelfth days of therapy (Series 1 and 2), the means before treatment and those occurring between the thirteenth day and the cessation of therapy (Series 1 and 3), and those obtained before and after treatment (Series 1 and 4).

From these Tables it can be seen that the hypoglycaemic effect of small doses of insulin is significantly increased during the early phases of deep

TABLE IV

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH DEEP INSULIN

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Fall of blood sugar (mg.)	t	2·40	1·53	2·22
	P	<0·01	>0·05	<0·025
	significance	+	−	+
Fall of blood sugar (%)	t	1·79	0·54	1·51
	P	<0·05	>0·25	>0·05
	significance	+	−	−
Fasting blood sugar (mg./100 ml.)	t	2·24	1·90	2·57
	P	<0·025	<0·05	<0·01
	significance	+	+	+
Eosinopenia (%) ..	t	6·75	8·69	7·57
	P	<0·005	<0·005	<0·005
	significance	+	+	+
Eosinophils (per c.mm.)	t	2·02	2·67	2·65
	P	<0·05	<0·01	<0·05
	significance	+	+	+
Plasma chlorides (mEq.)	t	2·68	0·91	1·03
	P	<0·025	>0·15	>0·15
	significance	+	−	−

TABLE V

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH E.C.T.

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Fall of blood sugar (mg.)	t	1·52	1·50	0·01
	P	>0·05	>0·05	>0·45
	significance	−	−	−
Fall of blood sugar (%)	t	0·97	0·37	0·34
	P	>0·15	>0·35	>0·35
	significance	−	−	−
Fasting blood sugar (mg./100 ml.)	t	1·94	2·67	1·35
	P	<0·05	<0·025	>0·05
	significance	+	+	−
Eosinopenia (%) ..	t	4·65	4·57	9·05
	P	<0·005	<0·005	<0·005
	significance	+	+	+
Eosinophils (per c.mm.)	t	4·21	2·60	1·33
	P	<0·01	<0·05	>0·20
	significance	+	+	−

insulin therapy. The mean fall of blood sugar in the groups treated with E.C.T. or modified insulin is similarly augmented, although in these the fall is not significant. Hence, increase in sensitivity to small doses of insulin is the rule rather than the exception with these treatments, and presumably, therefore, bears no relation to prognostic factors. However, there were individual exceptions to these overall results for the group, and these are presented in Table VII.

It can be inferred from the latter that increase of sensitivity during or immediately after treatment, following the previous demonstration of resistance to small doses of insulin, may still not be associated with improvement (Case 13), and that no increase

TABLE VI

SIGNIFICANCE OF THE DIFFERENCE BETWEEN MEANS DERIVED FROM TESTS ON PATIENTS TREATED WITH MODIFIED INSULIN

Indices	Statistical Criteria	Series 1 and 2	Series 1 and 3	Series 1 and 4
Fall of blood sugar (mg.)	t	1·36	1·10	0·61
	P	>0·05	>0·10	>0·25
	significance	−	−	−
Fall of blood sugar (%)	t	1·02	0·41	0·07
	P	>0·10	>0·30	>0·45
	significance	−	−	−
Fasting blood sugar (mg./100 ml.)	t	1·52	3·17	1·31
	P	>0·05	<0·005	>0·10
	significance	−	+	−
Eosinopenia (%) ..	t	1·75	3·38	2·11
	P	>0·05	<0·005	<0·05
	significance	−	+	+
Eosinophils (per c.mm.)	t	0·23	0·03	1·63
	P	>0·40	>0·45	>0·05
	significance	−	−	−

TABLE VII

RESISTANCE TO SMALL DOSES OF INSULIN IN RELATION TO THERAPY

Case No.	Illness	Before Therapy	5th to 12th Day of Therapy	13th Day to End of Therapy	After Therapy	Degree of Improvement
1	P	−	−	+	+	G.I.
4	P	+	−	−	−	G.I.
9	P	−	−	+	+	G.I.
12	P	+	+	+	+	G.I.
13	P	+	−	+	−	U.
14	P	−	−	−	+	U.
27	P	−	−	−	+	S.I.
28	N	+	−	−	−	N.A.
34	N	−	−	+	+	N.A.

P = psychotic illness. N = neurotic illness. + = positive incidence of insulin resistance. − = negative incidence of insulin resistance. G.I. = greatly improved, S.I. = slightly improved, U = unimproved. N.A. = not assessed.

of sensitivity during or immediately after treatment in a patient originally resistant to small doses of insulin in no way impedes improvement (Case 12). Moreover, the emergence of resistance to small doses of insulin in patients who were previously sensitive to the drug may or may not be associated with improvement (Cases 1, 9, 14, and 27).

The mean level of the fasting blood sugars showed a significant increase during and immediately after therapy with deep insulin and during the later stages of treatment with modified insulin and E.C.T., although the means of the fasting levels were raised even in those instances in which this increase was not statistically significant. There were no individual exceptions to these findings for the group.

The decrease of the mean eosinophilia accompanying insulin tolerance tests was statistically significant for all patients during and immediately after the cessation of therapy with deep insulin and E.C.T.,

but only during the later phases and immediately after the termination of treatment with modified insulin.

Similarly, a significant mean eosinophilia occurred during and immediately after the cessation of therapy with deep insulin, during but not immediately after the completion of a course of E.C.T., and not at all either during or immediately after treatment with modified insulin. The significance of individual mean eosinophilias was assessed by the strict criterion of Berkson, Magath, and Hurn (1940) which requires that any variation from the mean of a cell count should be at least twice the standard deviation of that mean to be significant. The presence or absence of a significant individual eosinophilia was correlated with the clinical status of the patient immediately after the completion of a course of therapy, and the findings are tabulated in Table VIII.

TABLE VIII

CORRELATION OF THE DEGREE OF EOSINOPHILIA WITH THE IMMEDIATE RESULTS OF THERAPY

Therapy	Eosinophilia	Degree of Improvement			Total
		Great	Slight	Unimproved	
Deep insulin	+	5	4	3	16
	−	0	2	2	
E.C.T. ..	+	1	3	1	5
	−	0	0	0	

+ =significant individual eosinophilia. − =insignificant individual eosinophilia.

Thus, of those patients treated with deep insulin, and of those manifesting individual significant eosinophilias, five were greatly improved, four slightly improved, and three unimproved, whereas, of those patients exhibiting no significant eosinophilia, two were slightly improved and two unimproved. The eosinophilia was significant for all patients treated with E.C.T., and of these one was greatly improved, three slightly improved, and one unimproved. Thus, in the groups treated with deep insulin or E.C.T. the patients exhibited either no eosinophilia or a significant moderate eosinophilia with a maximum mean of 250·4 eosinophils per c.mm. for those treated with deep insulin and a maximum mean of 125·2 eosinophils per c.mm. for those treated with E.C.T. No instances were observed of the very high counts of 1,000 eosinophils per c.mm. or more recorded by Shands and Menzer (1953) or Freeman, Jones, and Palmer (1954).

The relation of the eosinophilias to prognosis in the group receiving modified insulin was not elucidated, as not all these patients were having treatment exclusively for their mental symptomatology. However, there was an increase in the resting level of eosinophils during the early phase of therapy, although this mean increase was not statistically significant.

Of those patients treated with deep insulin and on whom the plasma chlorides were estimated, all showed an increase of these values except Case 17. In this patient they remained stationary during and immediately after therapy, and the patient remained unimproved as the result of treatment. Of the rest, one was greatly improved, two slightly improved, and three unimproved immediately after the termination of therapy. The mean increase of the plasma chloride values was statistically significant only during the fifth to twelfth days of therapy.

Discussion

From the results presented above it can be concluded that resistance to small doses of insulin occurs in schizophrenics in whom the diagnosis of oneirophrenia would be untenable. In addition, a decrease in resistance to small doses of insulin with concomitant clinical recovery may occur in schizophrenics during the course of therapy, and who, again, do not warrant a diagnosis of oneirophrenia. Furthermore, a decrease of insulin resistance may be unaccompanied by clinical improvement, whereas an increase of insulin resistance may be associated with recovery. More important still, if the groups as a whole were considered, an increase in the hypoglycaemic effect of small doses of insulin occurred during or after treatment, no matter whether therapy was with insulin or E.C.T., and hence these changes bear no particular relation to diagnosis or prognosis.

In addition, there was resistance to small doses of insulin in one patient suffering from a neurotic disorder before treatment, and in another during and after the completion of a course of modified insulin. Thus, resistance to insulin can occur both in neurotics and schizophrenics and in fact has been reported in other conditions, for instance, in patients suffering from the malignant phase of hypertension (Olsen and Nuetzel, 1950). This confirms the opinion of Mayer-Gross (1952) who could discover no positive correlation between the incidence of resistance to small doses of insulin and a diagnosis of oneirophrenia, a conclusion similarly endorsed by Lingjaerde (1952).

An increase of resting eosinophil cells accompanied treatment with insulin or E.C.T. and bore no clear-cut association to clinical improvement. These findings are in accord with those of Shattock

and Micklem (1952), who reported that an increase in the number of eosinophils occurred both in patients who recovered and in those whose clinical progress was disappointing. More recently, Shands and Menzer (1953) and Freeman and others (1954) have arrived at an identical conclusion.

The mean eosinopenia accompanying serial insulin tolerance tests decreased in magnitude during and after the termination of the various therapies, and it is relevant that Altschule, Parkhurst, and Tillotson (1949) reported that in man the response of the eosinophils to electrically induced convulsions decreased with frequently repeated "shocks", but that the response may return to its former level after a rest period of at least nine days. They further remark that their findings are reminiscent of the work of Hills, Forsham, and Finch (1948) who noted a diminished eosinopenia after daily injections of adrenocorticotropic hormone. Similarly, Sprague, Mason, and Power (1951) observed that a reduced eosinopenic response accompanied continued administration of cortisone.

Other results that mimic closely the findings presented in this paper have been reported by Masson (1941) who found, after exposing animals to various stressors, that the hypoglycaemic effect of insulin was considerably augmented during the stage of resistance of the general adaptation syndrome. He surmised, therefore, that the hypoglycaemic action of this hormone increases during adaptation to non-specific agents. An equivalent phenomenon has been recorded after lumbo-dorsal sympathectomy and interpreted as a manifestation of the general adaptation syndrome (Simeone and Vavoudes, 1948; Simeone, 1949). A transient eosinophilia was observed by White (1951) during the experimental production of the general adaptation syndrome in sheep, and Laragh and Almy (1948) and Johnson, Conn, Iob, and Coller (1950) have suggested that the eosinophilia following upon the stress of traumatic injury may be in some way linked with the adaptation syndrome. Last, Jordan, Pitesky, and Siegel (1950) noted that a diminished eosinopenic response accompanied adaptation to stress induced by adrenalin. Likewise, Jordan, Pitesky, Bond, Johnson, and Last (1950) observed a decreased eosinophil response in association with adaptation to stress. Hence the increased hypoglycaemic effect of small doses of insulin, the diminished eosinopenias, and the elevation of the level of eosinophils, have been observed during adaptation to stress or accompanying the continued administration of adrenocorticotropic hormone.

As for the other results reported in this paper, the increased values for fasting blood sugars recorded during treatment with deep insulin have been noted previously by Looney and Cameron (1937). In addition, Gellhorn and Safford (1948) found that the fasting blood sugar of rats was markedly augmented after 10 electro-shocks, but that after a further 14 electro-shocks the fasting blood sugar had declined again to normal values. However, insulin and E.C.T. are so-called stressors, and Selye (1950e) has noted that stress is accompanied by an initial hyperglycaemia succeeded later by hypoglycaemia, although eventually during the counter-shock phase, the blood sugar returns to normal and remains at, or slightly above, this level; that is, throughout the entire stage of resistance of the general adaptation syndrome. But the anterior pituitary and adrenocortical hormones are the major factors in maintaining a fasting blood sugar level (Long, 1952) so the raised fasting blood sugar values presumably reflect some altered activity of these endocrines. It is of interest, therefore, that Forsham, Thorn, Prunty, and Hills (1948) commented on an increase of the fasting blood sugar levels and a marked sodium and chloride retention following the administration of adrenocorticotropic hormone. Finally, Selye (1938) in experiments on over 700 hooded rats recorded that in the course of adaptation to stressors (cold, formaldehyde, and histamine) there was an initial decrease in the chloride content of the blood, with a subsequent return to normal or even to an increase above the normal values.

Thus, the increase in the hypoglycaemic effect of small doses of insulin, of fasting blood sugar levels and eosinophil cells, and the diminished eosinopenias and increased plasma chloride values that accompany the administration of a course of insulin or E.C.T. are seen also in association with the continued injections of adrenocorticotropic hormone or the development of the stage of resistance of the general adaptation syndrome. Hence these changes are best considered as being non-specific.

Summary

The presence of resistance to small doses of insulin in schizophrenics, or the disappearance of this resistance during treatment, has no diagnostic or prognostic worth. The same may be said for the increase, or absence of increase, of the values for the resting eosinophil cell counts before, during, or after therapy.

The increased hypoglycaemic effect of small doses of insulin, of fasting blood sugar levels and resting plasma chloride values, of increased eosinophil cell counts, and diminished eosinopenic response associated with the progress of treatment appear to be

non-specific and to represent tissue and biochemical adaptation to the repeated administration of insulin or E.C.T.

I should like to take this opportunity of thanking Dr. A. G. Duncan, the Medical Superintendent, for his kind permission to publish these findings.

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A PRELIMINARY REPORT ON A PERCEPTUAL MAZE TEST SENSITIVE TO BRAIN DAMAGE

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During an investigation into the clinical effects of prefrontal leucotomy, an attempt was made to design a simple psychological test procedure sensitive to organic damage to the frontal lobes. The preliminary results obtained with the perceptual maze test reported below suggest that it is sensitive both to cerebral damage in the frontal regions and to damage to the anterior temporal lobe. Because of the theoretical interest of this test further development and standardization studies will be undertaken. These involve a change in the format of the test material, and it seems appropriate to make now a preliminary communication describing the principles of the test and the clinical results obtained.

Description of the Test

The test material (Fig. 1) consists of 30 patterns each of which has a lattice background of paths or tracks. At a variable number of intersections dots are superimposed. In the original pattern the paths were white with red circles at the intersections and the background was black (Fig. 1a). In the new version the paths are interrupted lines and the dots are solid black circles (Fig. 1b, c, and d). In either version the subject is required to find in each pattern a pathway from bottom to top—or from top to bottom—which passes through the greatest possible number of dots. There are two restrictions. First, the subject must keep to the paths or tracks and must not cut across from one path to another. Secondly, at any junction point the pathway chosen by the subject must continue forwards, i.e., it may fork left or right but must not double back. Each pattern is so designed that there is only one correct series of dots through which the pathway can pass. In order that the subject may know when he has found a correct pathway, he is told the maximum number of dots which can be obtained in each pattern.

In a version which is being standardized, the individual items are printed together in a form suitable for administration as either a group or individual pencil and paper test. All the preliminary work, the results of which are reported here, was however carried out with the original type of pattern (Fig. 1a). These patterns were drawn up individually on separate sheets of paper. After preliminary trials 30 items were selected to form a scale of steadily increasing difficulty. Patterns were chosen on the basis of their difficulty relative to the size of the background trellis.

Administration of the Test

Each subject was shown a sample pattern (Fig. 1a) and was given the following instructions: "Here is a pattern; you have to find the path from bottom to top or top to bottom which passes through the most red circles. You must stick to the white paths and at each fork you can go either left or right but you must not double back." These points were illustrated on the demonstration pattern and repeated if the subject did not clearly understand them. This wording was not rigidly adhered to and if the subject's understanding was thereby aided concrete analogies, e.g., grass and paths, were used. The subject was then told that he would be shown other similar patterns and that for each of these he had in the same way to find a path which passed through the greatest number of circles. It was added that he would be told for each pattern how many circles it was possible to obtain. He was also told that he would be given plenty of time—one minute—for each pattern but that he should attempt to find the correct path as quickly as possible. In order that the test material could be re-used the subject was not allowed to draw on the patterns but was asked to show the examiner the correct path with a wooden stylus. The test was then given in accordance with the above instructions and a record was kept of the time—to the nearest five seconds—taken to solve each pattern. When the subject failed to find the correct answer within a minute he was shown the solution by the examiner and was then given the next pattern. The test was continued until the subject failed to solve four consecutive patterns. Because early experience had shown that the extra time did not add proportionally to the subject's ability to solve individual patterns the test was stopped when the subject failed to solve four consecutive patterns each within 30 seconds. This materially reduced the amount of time wasted due to subjects scoring lucky hits after they had already reached their ceiling. Until the test was stopped a record was kept of the time taken on all solutions achieved within the one minute time limit. The test was scored on the basis of one point for each pattern correctly solved with an additional credit of a further point if it was solved within 30 seconds.

Subjects

In its original form the test was administered to the following groups of subjects: Group A, patients who were examined with the maze both before and after leucotomy or temporal lobectomy; Group B, patients who were attending the leucotomy follow-up clinic, most of whom had been examined in the psychological department before and after operation but who were examined with the maze only after operation; Group C, other patients from the neurological and psychiatric wards of the hospital.

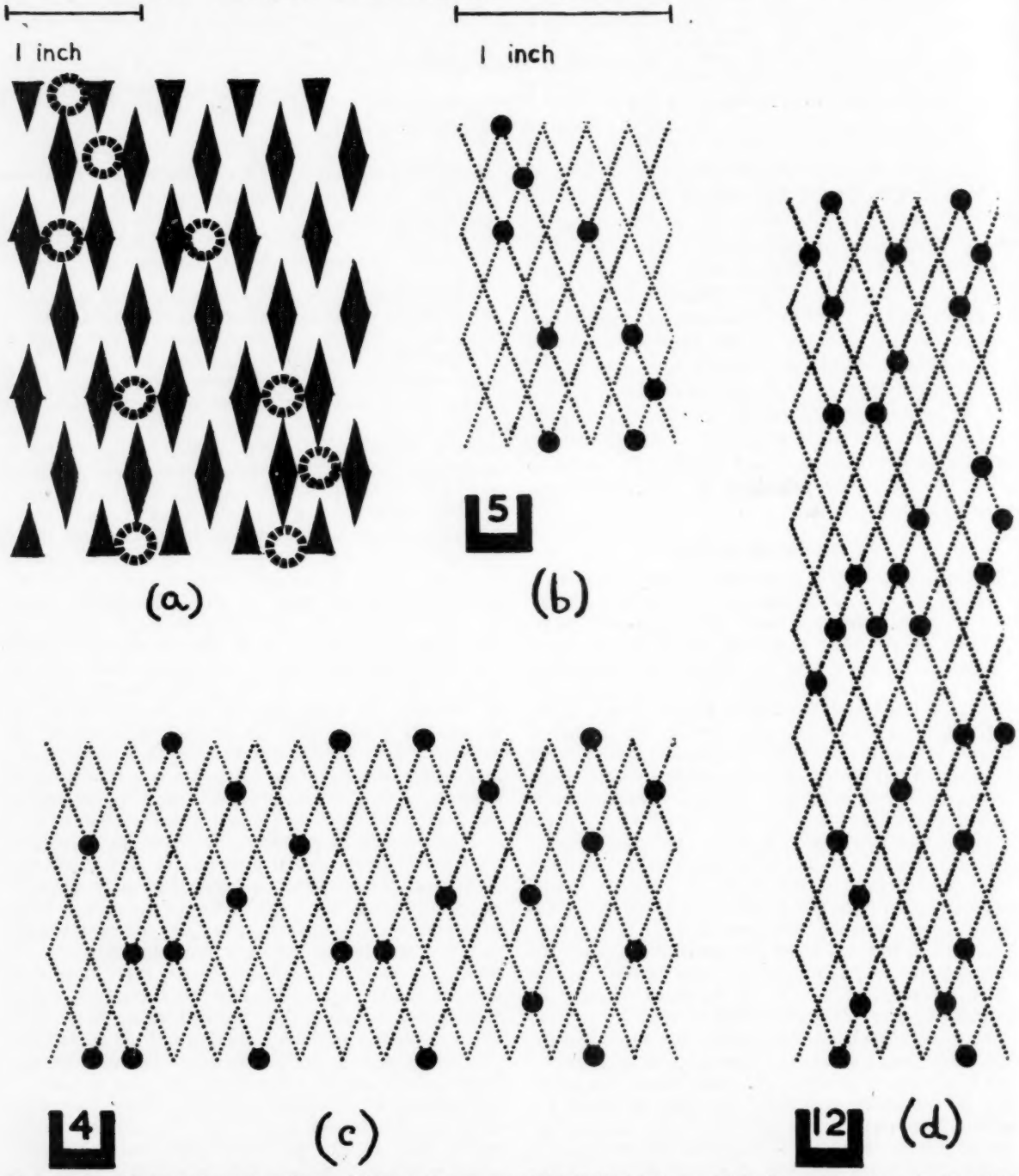


FIG. 1.—Reproductions of sample patterns: (a) Type of maze used for individual test reported in the present paper; in the original material the rings were red. (This particular pattern was used as a demonstration one.) (b) The same pattern in the modified format. (c) and (d) Sample patterns to illustrate that the complexity can be increased by enlargement in both the horizontal and vertical dimensions. The photographic reduction for the two types of pattern is different, the original sizes being as indicated.

Results

Group A : Temporal Lobectomy and Prefrontal Leucotomy.—Because a modified operation is now the treatment of choice in patients who come to leucotomy, 14 of the 20 subjects in this group had partial leucotomies. Only one patient who suffered from intolerable pain associated with an inoperable carcinoma had a standard leucotomy. The remaining five patients had an operation involving the partial removal of one temporal lobe. All the patients in this group were tested before operation and again not less than a fortnight post-operatively. Of the 14 patients subjected to a partial leucotomy 12 achieved a better score post-operatively. The mean gain for these 14 patients was $10{\cdot}1 \pm 2{\cdot}95$ points. This contrasts markedly with the results obtained with the five patients who underwent an operation on the temporal lobe. Of these, four performed less well post-operatively, the mean loss for all five subjects being $8{\cdot}6 \pm 6{\cdot}28$ points. The groups are small but the difference between them is statistically significant ($t = 3{\cdot}05$, $P < 0{\cdot}01$). Although four of the temporal lobe cases had a partial or complete quadrantic field defect their failure on the test did not appear to be due to this disability. Thus the one patient who had no field defect was also reported as having no visuospatial disability following the operation ; nevertheless his score was worse post-operatively. Conversely, the one temporal lobe patient whose performance was better post-operatively did have a left upper quadrantic field defect. This observation—that a small amount of damage to one temporal lobe disturbs performance on this test more than does a modified bilateral leucotomy—needs confirmation. It is, however, in accord with Milner's contention that damage to a temporal lobe causes impairment of high level visual skills (Milner, 1954).

Group B : Post-Leucotomy.—There were 36 patients in this group, all of whom were examined at least three months after leucotomy. Twenty-two of these patients had had a standard operation of the type described by Freeman and Watts (1942) ; 13 patients had had some form of partial leucotomy, and, of these, seven had had a modified operation by a lateral approach, five a rostral leucotomy, and one a cingulectomy ; one patient, who had had a standard leucotomy elsewhere and who was subsequently submitted to a partial operation here because it was considered that the first operation had failed, has been omitted. The mean score for the 22 patients who had had a full leucotomy was $18{\cdot}5 \pm 2{\cdot}26$ while that for the 13 patients who had a partial operation was $23{\cdot}8 \pm 3{\cdot}28$. This difference does not reach a satisfactory level of statistical confidence ($t = 1{\cdot}10$, $P > 0{\cdot}1$). The results are, however, suggestive, and examination of the case records of the patients showed that two of the patients in the partially leucotomized group were anomalous. One had proved to be suffering from a presenile dementia and the second had had a post-operative collapse attributed to a complicating cerebral thrombosis. If these two patients are excluded, then the remaining 11, who had only a partial operation, performed significantly better (mean score $26{\cdot}9 \pm 2{\cdot}76$) than those who had had a full leucotomy (mean score $18{\cdot}5 \pm 2{\cdot}26$, $t = 2{\cdot}31$, $P < 0{\cdot}05$). That this difference is not attributable to age differences between the groups has been shown by an analysis of covariance, and that it is not due to original differences in intellectual level has been similarly demonstrated on the 29 patients for whom data as to the pre-operative intellectual level were available. This observation that a standard leucotomy impairs the maze performance more than does a modified leucotomy does not conflict with the previous observation that patients retested after a modified leucotomy showed improved scores. This improvement would be partly due to practice effects and partly due to the reduction of emotional disturbance which followed the operation.

While the maze test was being administered to these patients attending the leucotomy follow-up clinic it was noticed that there was an apparent correlation between success on this test and successful post-operative adjustment. In order to test Porteus' claim (Porteus, 1952) that maze type tests may be sensitive to " social intelligence ", Mr. E. G. Glithero, Psychiatric Social Worker to the Department of Psychiatry, who was completely unaware of the results obtained with the test, was asked to assess the success these patients were making of their post-operative social rehabilitation. He very kindly undertook this rather difficult task and succeeded in producing for the group for whom psychological test results were available, a rank order of social adjustment. There is a significant relationship between this rank order of social adjustment and that of success on the maze. In assessing the strength of this relationship Kendall's tau has been used : ($tau = 0{\cdot}308$, $P < 0{\cdot}02$, $n = 31$). The value obtained for the relationship between pre-operative intelligence, as measured by the vocabulary score, and post-operative social adjustment is much smaller and not significant ($tau = 0{\cdot}156$, $P > 0{\cdot}05$).

Group C : Other Patients.—Unfortunately it did not prove possible to retest after the lapse of an appropriate interval the majority of patients in this group. Most of them were, however, also tested with the vocabulary and Koh's blocks sub-tests of

the Wechsler Bellevue scale (Wechsler, 1944), and the results obtained with these subjects have therefore been used together with the pre-operative findings obtained with the subjects of Group A to derive product moment correlations between the maze scores obtained and the two Wechsler sub-tests. The correlation between the maze score and the vocabulary score is $+0{\cdot}462$, $P < 0{\cdot}01$ ($n = 43$). That between the maze and Koh's blocks is $+0{\cdot}738$, $P > 0{\cdot}001$ ($n = 43$).

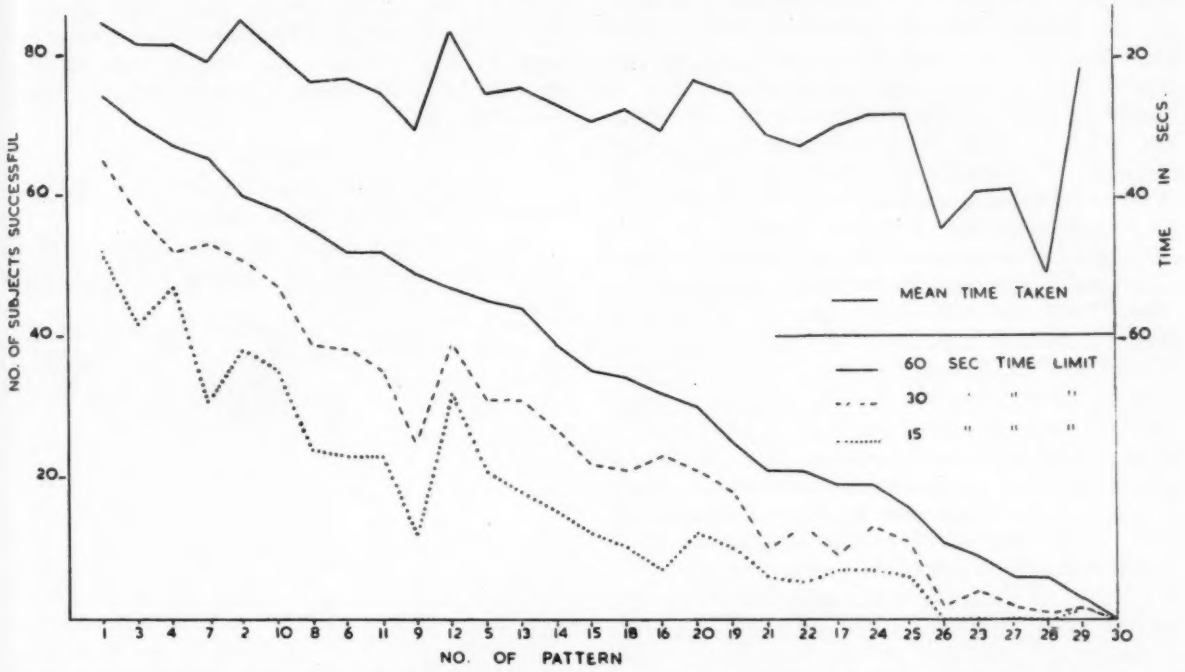
Performance on psychological tests sensitive to organic cerebral damage tends to deteriorate with increasing age and it seemed worth while to study the relationship of this variable to the maze scores. For this group of subjects the product moment correlation with age for the vocabulary scores was $-0{\cdot}040$ ($P > 0{\cdot}1$), for the Koh's blocks scores it was $-0{\cdot}575$ ($P < 0{\cdot}001$), and for the maze it was $-0{\cdot}500$ ($P < 0{\cdot}001$). The finding that the vocabulary score is virtually independent of age and that the Koh's block test is not is a well attested one (Jackson, 1955). The observation that the maze test performance with this group deteriorates with increasing age is in agreement with and supports the finding that this test is sensitive to organic deteriorative processes. It is not on the present material an independent observation: the group is not a normal sample and the frequency of organically determined psychological illnesses is greater amongst the more elderly patients. Similar considerations may have tended to produce a rather high correlation between the maze test scores and the Koh's block scores but it is worth observing that the partial correlation between these tests when the vocabulary score is held constant is still high ($r_{mk.v.} = +0{\cdot}589$). This suggests that the maze test may, like Koh's test, be a good test of spatial abilities.

The results obtained with Group C subjects together with those obtained from the patients in Group B and those obtained on first testing the patients in Group A have been used further in studying other characteristics of the maze patterns. The results for all the 87 subjects are presented graphically in Fig. 2. In this figure each co-ordinate refers to an individual pattern. These are arranged along the abscissa in order of increasing difficulty according to the number of successful solutions achieved during the 60 seconds allowed for each pattern. The diagram also shows the number of patterns which were achieved within the time limits of 30 seconds and 15 seconds respectively. It will be apparent that an increase in the amount of time allowed for each puzzle does not result in a proportionate increase in the number of subjects achieving a solution. For the test as a whole the following results were obtained: when 15 seconds was the time allowed, 497 items were solved; in 30 seconds, 762 items were solved; and when 60 seconds were allowed, 1,064 items were solved. It must be remembered that not all the subjects attempted the more difficult patterns as the test was discontinued after four consecutive failures. However, it was a commonly reported subjective experience that the correct pathway was seen either fairly rapidly or only with considerable difficulty. This all-or-none effect does seem to be characteristic of the test and may be related to another frequently reported tendency, namely, that subjects experienced difficulty in reconsidering paths that had already been rejected. In order to examine this point further the mean time for the successful solution of each item has been calculated. Again these figures have a limited value as there was an upper time limit of 60 seconds. The results have been plotted graphically (upper curve in Fig. 2) and it can be seen that the length of time taken to solve individual items increases very slowly when it is compared with increase in difficulty expressed as the number of subjects successfully solving the item within the time limit. This is particularly obvious over the median half of the test where the observations are likely to be the most reliable. Thus pattern No. 8 (seventh in order of increasing difficulty) was passed by 55 of the 87 subjects in a mean time of 24·2 seconds while pattern No. 25 (twenty-fourth in order of increasing difficulty) was passed by 16 subjects but in a mean time of 27·4 seconds. These 16 more able subjects solved pattern No. 8 in a mean time of 18·1 seconds.

Reliability of the Test

Although it has not proved possible to estimate the reliability of the test on a control group, evidence that this is high can be adduced from two independent observations. First the patients in Group A were re-examined on a second occasion after their operation. The interposition of an additional variable—type and extent of operation—will only dilute the reliability and it is likely that under more favourable circumstances the test-retest correlation would be higher than that observed ($r = 0{\cdot}813$, $P < 0{\cdot}001$, $n = 18$). Secondly the order in which the patterns were presented to the present group was determined by a preliminary pilot study with subjects the majority of whom were normal volunteers. If the correlation between the rank order of the items as determined in the pilot study and that observed in the present investigation is high it will indicate that the patterns are consistent in their

FIG. 2.—Relative difficulty of the different patterns. The patterns are arranged along the abscissa in an order of difficulty derived from the present investigation. The numbers of the patterns represent the order in which they were presented and this is the same as the order of difficulty determined in a pilot study. The ordinates for the three lower curves represent the number of successes in 15, 30, and 60 sec. respectively. The upper inverted curve shows the mean time in seconds taken to solve each test.



relative difficulty even when tested against samples from different populations. In Fig. 2 the patterns are arranged along the abscissa in an order of difficulty which is derived from the number of times each pattern was passed within the 60-second time limit during the present study. The numbers also represent the order of difficulty as determined in the pilot study. The relationship is clearly a close one (tau = 0·87).

Discussion

While the results so far obtained with this test are limited in range they indicate that the material is internally consistent and capable of giving repeatable results. That it may be sensitive to organic frontal lobe damage is indicated by the fact that it distinguishes between two groups of subjects who have been subjected to leucotomy operations of different extent. It appears to be unexpectedly sensitive to small lesions in the temporal region. It has also been shown that although the task is essentially a visuospatial scanning one, in which the need for formal intellectual processes is apparently absent, it correlates quite highly both with verbal and performance intelligence tests and with an independent assessment of post-operative social adjustment. Finally, test performance correlates negatively with increasing age.

The theoretical interest of this test lies in the fact that there is a high correlation between intellectual ability and test achievement, although once the instructions have been mastered the performance is essentially a perceptual skill and does not involve any formal logical processes. Thus it has been pointed out that successful solution of the task involves the ability to reject from the perceptual field irrelevant areas of the pattern and that once the correct pathway has been discovered it seems subjectively to dominate the perceptual field (Allan, 1954). It is of course true that the discovery of the correct path can, like the task of finding the ball in the field, be achieved by a rigorously pursued sequential search. Nevertheless most subjects feel that a solution is achieved more rapidly by a perceptual scanning of the material. As the difficulty of the patterns increases so does the tendency for this type of scanning behaviour to give way to the more sequential type of trial and error searching. It is suggested that superior performance on this type of maze is correlated with the ability to maintain a perceptual set in the face of material of steadily increasing complexity. In other words, the individual's performance reflects the size of the perceptual unit with which he is able to deal.

In this connexion it is interesting to note that Hick (1952), applying information theory to per-

ceptual tasks, has suggested that the rate of gain of information which can be achieved in perceptual tasks is in order of five bits a second. Although the maze test consists of a complex of binary situations, i.e., the presence or absence of a dot at sites which are distributed in a regular manner over the perceptual field, it cannot easily in its present form be treated in terms of information theory. Nevertheless, preliminary inspection suggests that this type of display may enable information to be taken up at a considerably greater rate than that observed in the more restricted situations studied by Hick (1952); this suggestion, though tentative, would be in accord with the observations of Klemmer and Frick (1953) on the assimilation of information from dot and matrix patterns. A further observation of considerable theoretical interest is that performance on the multiple choice maze seems to be easily impaired by emotional disturbance. The improvement which occurred in patients who responded satisfactorily to a modified leucotomy is almost certainly not entirely due to practice effects but partly to the reduction in emotional disorganization which generally accompanies a successful operation. It is in fact a common observation that emotional distress does interfere, often seriously, with the exhibition of intelligent activity in ordinary social situations. Further, Raven has pointed out (personal communication) that some reports that the reliability of his matrices is not always exceptionally high may only be a reflection of the fact that this test is sensitive to day-to-day fluctuations in intellectual efficiency.

That many valid and useful performance tests of intellectual ability measure the range of acquired intellectual acts and the speed with which these sets can be applied rather than the available integrative ability is a point not often emphasized. Cattell in distinguishing between these two types of intellectual performance called the first " crystallized " and the second " fluid " (Cattell, 1943). This author points out that it is fluid intellectual ability which declines most rapidly with age and which is most susceptible to brain injury. Similar considerations apply to the impairment of test performance by emotional disturbance. Halstead (1947), using physiological discriminative tests with a high " G " loading, found that his " impairment factor " was present almost as markedly before leucotomy as after. It may be as much this sensitivity to emotion as a practice effect which causes scores on the present test to improve after modified leucotomy. In addition to this inherent susceptibility to emotion of tests requiring " fluid G " the multiple choice maze appears to be in itself a neuroticizing situation. Because of the arrangement of the material it is not possible, in the absence of gross disorientation, to make an incorrect answer and consider it to be correct: the puzzles appear deceptively easy and subjectively a feeling of frustration can appear and increase rapidly when the subject has searched thoroughly, as he thinks, a matrix, without finding the correct path.

Summary

A multiple choice maze suitable for use as a clinical psychological test is described.

The preliminary results reported suggest that the test is sensitive to cerebral damage localized to the temporal or frontal lobes.

The performance of subjects on this test correlates significantly with estimations of their intellectual abilities derived from their performance on the vocabulary and Koh's block sub-tests of the Wechsler intelligence scale and with an independent estimate of success in post-leucotomy social adjustment. It correlates negatively with increasing age.

It is suggested that the success achieved in dealing with the test material may reflect the subject's ability to maintain a perceptual set in the face of material of steadily increasing complexity.

My thanks are due to the physicians and surgeons of the National Hospital who kindly allowed me to examine patients under their care, and to Professor O. L. Zangwill and his colleagues for access to and permission to use the results of tests undertaken in the Department of Psychology. To Dr. E. A. Carmichael, Dr. E. T. O. Slater, and Professor O. L. Zangwill I am indebted for criticism, advice, and continual support. I am also particularly grateful for stimulating discussion and help given by Miss M. D. Allan and Mr. M. F. Piercy. Miss M. A. Crosskey and Mrs. C. Lawrence assisted with the art work and the administration of the tests and undertook the major part of the statistical calculations. To Dr. P. Armitage I am grateful for statistical advice.

The material for this test, the N.R.U. Multiple Choice Maze, is not, at the time of writing, available in a standardized form suitable for routine use. Should it be required for research work, both the individual version and a form suitable for group administration can be obtained through the Medical Research Council's Neurological Research Unit at the National Hospital, Queen Square, London, W.C.1.

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HEAD INJURY AS A CAUSE OF INTERNAL CAROTID THROMBOSIS *

BY

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Thrombosis of the internal carotid artery with neurological signs may develop after direct violence to the wall of the artery in the neck. This has been known at least as far back as the last century and calls for little comment. A description of two such cases was published in 1936 by Caldwell, who warns against the error of attributing to concomitant head injury the symptoms and signs which develop as a result of traumatic thrombosis of the internal carotid artery in the neck.

Ramsay Hunt first called attention to the occurrence of spontaneous thrombosis of the internal carotid artery in 1914. He and most successive authors conclude that arteriosclerosis is the most important aetiological factor. In this communication evidence is produced and the mechanism suggested whereby, in some cases of internal carotid thrombosis, a major or minor head injury may be instrumental in precipitating the thrombotic process. The clinical evidence of such a thrombosis may be immediate or delayed and in the latter event may present, some time after the injury, as a case of " spontaneous " thrombosis.

Of the other known aetiological factors, thromboangiitis obliterans has been discussed by Davis and Perret (1947) and Cloake (1951). Thrombosis occurring after rupture of an intracranial aneurysm has been recorded. Only two cases are established in the literature in which a thrombotic process resulted from a head injury. One of these cases was described by the late Sir Hugh Cairns (1942) and he quoted another case under the care of Löhr. It is of interest that in these cases thrombosis occurred in the intracranial segment of the artery. The present series consists of six such cases ; in five, a major head injury, and in one, minor trauma to the skull, are held responsible for the development of thrombosis of the intracranial segments of the artery.

Case Reports

Case 1 (4717/53).—A woman, aged 54, was admitted unconscious following a road accident. She had a haematoma of the left orbit with chemosis. There were no abnormal neurological signs. On the following day a cerebrospinal fluid rhinorrhoea was noticed which subsided in two days. On the fifth day after the injury she was conscious and capable of sensible conversation and again no abnormal neurological signs were elicited. On the seventh day she became drowsy. Within two hours she developed dysphasia and paresis of the right arm. Shortly afterwards she became unconscious. She was transferred to the Neurosurgical Unit and the usual three sets of burr-holes were made. On the left side about 20 ml. of yellow subdural fluid was aspirated. The brain was a few millimetres away from the dura on both sides and the intraventricular pressure was subatmospheric. The left hemisphere felt somewhat softer than the right to the exploring cannula. On lumbar puncture cloudy fluid containing pneumococci was found. The meningitis was vigorously treated but she continued to deteriorate : the right leg became paralysed as well as the right arm, and she died 13 days after the injury.

Necropsy.—A little purulent exudate was found in the cisterna ambiens. There was a linear fracture through the left cribriform plate extending posteriorly across the base of the left anterior clinoid process and also down into the body of the sphenoid. The dura over the cribriform plate showed a minute tear. The frontal and ethmoidal sinuses were healthy, but there was a small amount of mucopus in the sphenoidal sinus.

The left hemisphere was softened. The basilar, middle cerebral, and both internal carotid arteries showed a moderate degree of atheroma. The left internal carotid artery was thrombosed throughout the length of its intracranial portion as far as its bifurcation. At the point where the artery pierced the dura of the cavernous sinus the thrombus was firmly adherent to the wall at the site of an atheromatous plaque. Above and below this point the thrombus was softer and only loosely filled the lumen. There was no thrombus in the carotid arteries in the neck. Microscopic section at the site of adherence of the thrombus did not show any sign of infection in the arterial wall.

Case 2 (5700/54).—A man, aged 42, fell off a moving bus. He was unconscious, restless, but had no obvious neurological signs. There were minor facial injuries and orbital haematomata. A cerebrospinal fluid rhinorrhoea was noticed. Two days later he became more

* A shortened version of this paper was read before the Society of British Neurological Surgeons in December, 1954.

deeply comatose and a right hemiparesis was discovered. He was transferred to the Neurosurgical Unit and diagnosed as having an internal carotid thrombosis but exploratory burr-holes were made and excluded intracranial haemorrhage. He died 24 hours later.

Necropsy.—The skull showed a fracture similar to that described in Case 1. There was no infection. The left hemisphere was soft. The left internal carotid artery was occluded by a thrombus throughout the intracranial segment and this extended into the neck to a point 5 cm. above the carotid sinus. Distally the thrombus entered the left middle and anterior cerebral arteries. Both internal carotid arteries showed patches of atheroma in the region of the carotid sinus but there was no sign of thrombus formation there. The peripheral vessels, heart, and all other organs were normal. There was, in particular, no evidence of primary thrombus formation from which an embolus could have originated.

Case 3 (5850/54).—Eight years before, at the age of 32, this man fell and hit the left side of his head. He was not unconscious and after a time he continued his work. He went to bed that night feeling well but when he woke up the next morning he found the left side of his body paralyzed. Later he noticed anosmia and became aware of inability to see objects on the left side. In the course of a few months the leg partially recovered and he could walk. There was no recovery in the arm or in the hemianopia. On admission to the Neurosurgical Unit, eight years after the accident, right carotid angiography showed the characteristic arrest of the dye in the internal carotid artery 1·5 cm. above its origin. Left carotid angiograms showed filling of the left cerebral tree and also filling of the right anterior and middle cerebral arteries, the latter being only scantily visualized.

Case 4.—This patient was under the care of Mr. R. A. Money, of Sydney, Australia, who kindly provided the clinical data and permitted the publication of the case in this series.

A man, aged 32, was involved in a car collision in November, 1952. He received frontal injuries with a laceration of the forehead and lost consciousness. When he recovered he walked half a mile for help. He was then admitted to a local hospital and was found to be quite rational. The next day his condition deteriorated, he became unconscious, and developed, in the course of a few hours, a left hemiplegia. Five days after the injury he was admitted under the care of Mr. R. A. Money. He was stuporose and had a complete flaccid left hemiplegia with impairment of sensation on that side. An electroencephalogram indicated marked damage to the right side of the brain and suggested that a subdural haematoma might be present. Angiography by percutaneous and cut-down methods showed a complete obstruction of the right internal carotid artery about 1 in. above the carotid sinus. He was given heparin and a series of stellate ganglion blocks were performed without giving neurological improvement. During 1953 sufficient power had returned to the left leg to allow him to walk with an appliance. In April, 1953, he had an epileptic attack and fits recurred at odd intervals. An electroencephalogram in 1954 revealed slow waves originating from the right hemisphere. There was no further recovery in the limbs.

Case 5 (5053/53).—A woman, aged 69, was knocked down by a bicycle in August, 1953. She lost consciousness for about 15 minutes. She was admitted to the local hospital within 30 minutes of the accident where she was found to be slightly confused, the only abnormal neurological sign being a left facial weakness. The next day her conscious level deteriorated and she developed a left hemiparesis. An epileptic fit was reported. She was admitted to the Neurosurgical Unit on the third day after her injury.

On admission she was conscious but disorientated and emotionally labile. The pulsation of the right temporal artery was more pronounced than on the left. She had bilateral orbital haematomata and a laceration over the left eyebrow. The left pupil was slightly larger than the right but reacted to light. The optic fundi were normal but she showed an attention defect in the left homonymous fields. She had a left facial weakness and a complete left hemiplegia, the tone being increased to a greater extent in the arm than in the leg. She was unable to find the left limbs without looking for them and she had a complete astereognosis, tactile inattention, and transposition of painful stimuli into the space in front of her. A diagnosis of right internal carotid thrombosis was made. She made slow but gradual progress and on discharge, some weeks later, the power of the left limbs was nearly normal although the other abnormal signs persisted. For humanitarian reasons, the very great temptation to perform angiography was resisted. The diagnosis remains clinical.

Case 6 (4662/53).—A woman, aged 28, received a severe left frontal and temporal head injury with coma, bilateral proptosis, and orbital haematomata. A loud bruit was audible over the left eye and could be abolished by compression of the left carotid artery. A left-sided extradural haematoma was evacuated without any improvement in her condition. A few hours later the bruit was no longer present and she developed a right hemiplegia. She died shortly afterwards and post-mortem examination was refused. The clinical evidence is very strong indeed, however, that thrombosis of the internal carotid artery followed upon a traumatic arteriovenous fistula within the cavernous sinus.

Clinical Considerations

These cases provide interesting material for speculation upon the clinical progress of some confusing head injuries. A patient, after a lucid interval, may show deterioration in the conscious level accompanied by the onset of focal signs. Exploration for massive intracranial haemorrhage may prove negative. The brain is not under tension ; on the contrary, it may appear atrophic or one hemisphere may be softer than the other. The patient may improve and be left with some greater or lesser disability. The diagnosis made may be one

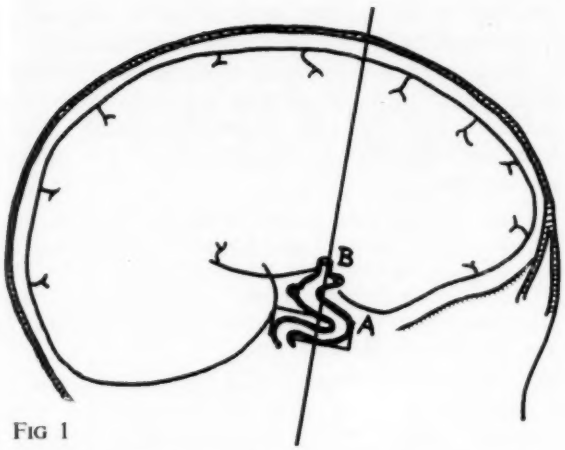

FIG 1

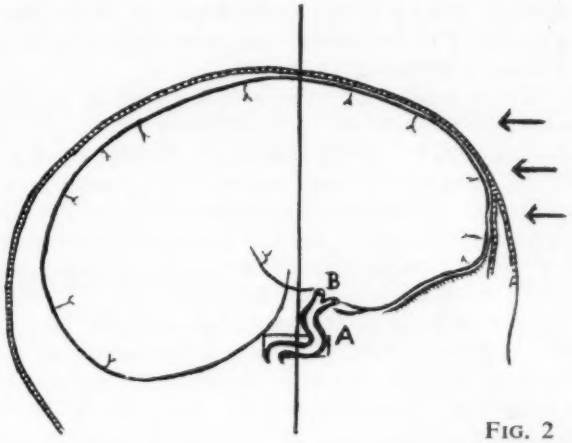

FIG. 2

of post-traumatic apoplexy or thrombosis of the middle cerebral artery or one of its branches, particularly if the patient is elderly. Internal carotid thrombosis, which is possibly the real cause, will not be diagnosed.

Anatomical and Pathological Considerations

Analysis of the foregoing cases suggests that thrombosis of the internal carotid artery took place as a result of trauma to the intracranial segment and in the two cases examined after death a fracture of the floor of the anterior fossa was found in close proximity (similar to the case described by Cairns). In all cases the main impact was frontal. Particular attention is drawn to the fact that in Case 1 the thrombus was firmly adherent to the wall at the point of emergence of the artery from the cavernous sinus. Here the artery is anchored by the embracing dura mater. This point, too, marks the centre of a variable "syphon", the distal end of which curves backwards and upwards and forwards before the artery ends by dividing into the anterior and middle cerebral arteries. These soon become fixed to the brain (Fig. 1). It were as though nature provided this slack segment to take the stress should the artery at any time be subject to movement.

From experimental work, and other observations, we know that when a force is applied to the head there is a certain amount of movement of the brain within its coverings. It may be a violent movement, as in severe injuries, or of lesser degree in minor injuries. It would appear, therefore, that the distal segment of the internal carotid artery moves with the brain, to which it is tethered by its terminal branches, while the more proximal end remains immobile at the point where the artery leaves the cavernous sinus (Fig. 2). It is submitted that at this latter point the artery is subject to shearing strains. Such strains, more so if the artery is sclerotic, may well be the precipitating factor in the formation of a thrombus. In the elderly patient with some cerebral atrophy, it is reasonable to suppose that the range of cerebral movement would be increased. Any strain to which the artery may then be subjected would likewise increase, and would occur at a time when the ageing vessels are less able to compensate for such a strain.

It seems highly probable that, particularly in the younger patient, the same mechanism may induce a spasm of the internal carotid artery which, for a time, may mimic a true thrombosis both clinically and on angiography. Connolly (1954) told of such a case under his care. The same interpretation was applied to one patient in this unit who unfortunately was referred too late for the angiography to be conclusive.

Discussion

Cloake (1951) states ". . . There are two sites of thrombosis, one near the point of origin of the vessel, the other in the intracranial portion close to its termination." Fisher (1951) believes that the first portion of the internal carotid artery is particularly liable to atheroma and that spontaneous thrombosis occurs just distal to the carotid sinus. The commonest site of internal carotid thrombosis in cases reported in the literature appears to be in the neck, particularly if the diagnosis is made by angiography. It is also probable that a thrombosis which begins in the intracranial segment might sometimes spread proximally to the region of the bifurcation. This has been reported in the literature following rupture of an aneurysm of the internal carotid artery, and two cases have been encountered in this Unit. Such a retrograde spread is finally arrested at about 1 to 2 cm. above the carotid sinus, because of the pounding of the blood as it whirls in and out from the sinus. This produces the

familiar angiographic appearances in those who survive. The thrombosis may not reach this level, however, before death occurs.

When there is thrombosis of the internal carotid artery after a head injury there may be early clinical evidence of it. Alternatively, for reasons of circulatory dynamics and anatomical channels of collateral circulation, such evidence may not be apparent for weeks, months, or years afterwards, the trauma being forgotten or discounted. In addition to the six cases described here, 12 other cases of internal carotid occlusion were collected in this hospital. Two of these followed rupture of a berry aneurysm, two were embolic, and eight were grouped as "spontaneous". Two of the latter gave a clear history of head injury 10 months and 10 years before the onset of signs.

Summary

Six cases are reported of carotid thrombosis and hemiplegia occurring as a delayed complication of head injury.

The possible mechanisms are discussed.

The primary site of thrombosis may more commonly occur in the intracranial segment than was previously supposed and may spread in a retrograde fashion into the neck.

Delayed symptoms after a head injury with angiographic evidence of an apparently primary cervical occlusion may give rise to a diagnosis of "spontaneous" internal carotid thrombosis.

Some confusing clinical syndromes following a head injury and suggesting massive intracranial haemorrhage but with negative surgical findings may be explained by thrombosis of the internal carotid artery.

I wish to express my grateful thanks to Mr. A. S. Kerr, senior surgeon of this Unit, for his encouragement and helpful suggestions. I am indebted to him and to Mr. R. H. Hannah for permission to publish cases under their care. I am also indebted to Dr. M. Wodzinski for the post-mortem examinations.

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Addendum

Since this paper was submitted for publication, a further case has been under treatment, a woman, aged 51, who sustained a frontal head injury with a fractured base, which gave rise to a thrombosis of the intracranial segment of the left internal carotid artery four days after the injury. The position of the thrombus and of the fracture were verified at necropsy.

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REPORT OF A FAMILY SUFFERING FROM FRIEDREICH'S DISEASE, PERONEAL MUSCULAR ATROPHY, AND SCHIZOPHRENIA

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Despite the many clinical and pathological data which have accumulated about the heredo-familial ataxias, Gardner's comment on Friedreich's disease almost 50 years ago, that ". . . the chief point to bear in mind about its aetiology is the tendency it shows to run in families" (Gardner, 1906), remains true of the group today. In consequence, the knowledge to be derived from the investigation of family pedigrees assumes great importance in the study of these disorders.

Unfortunately for the purpose, the heredo-familial ataxias are relatively uncommon affections of the central nervous system. Kinnier Wilson (1940) could find no more than 73 cases of Friedreich's disease among all patients attending the National Hospital, Queen's Square, from 1909 to 1925, i.e., about 0·4% of all admissions, and Sjögren was able to find only 188 cases in the records of six large Swedish clinics surveyed over at least 23 years (Sjögren, 1943). In her authoritative monograph on Friedreich's ataxia and spastic paraplegia, Julia Bell included a review of pedigrees in the world literature up till 1939 (Bell and Carmichael, 1939). She mustered 319 pedigrees in all, including 46 which were personally investigated; of these 136 were of hereditary ataxia, 72 of spastic ataxia, 35 of hereditary and spastic ataxia combined, and 74 of spastic paraplegia, two being unclassified. Only 69 of these family trees, however, included five or more afflicted persons, and this limitation handicaps the study of the rich variety of abortive and intermediate forms of the clinical pictures encountered.

This paper presents an account of a large, hitherto unpublished pedigree of one family displaying a number of neurological variants. In addition, several members of the family suffered from psychiatric disabilities; the mental state of the propositus in particular was clearly schizophrenic and of considerable interest in view of the renewed attention which has recently been paid to the association between that mental illness and Friedreich's disease.

Case Histories

Case II 28.—A. B., a man aged 53, was transferred to the Maudsley Hospital in February, 1953, from a metropolitan observation ward where a diagnosis of schizophrenia had been made. One month before admission he had become worried at the prospect of his daughter's forthcoming parturition. He appeared depressed; he refused to go to work and behaved peculiarly, often talking incomprehensibly to objects in the room.

Personal History.—This was the third time the patient had been admitted to hospital on account of mental symptoms. Coming from a working-class, south-east London background he had led a quiet, otherwise uneventful life which, until the outbreak of World War II, had been clouded by unemployment. For the past decade he had been working for the L.C.C., recently as a lavatory attendant.

Medical History.—Medically he had been aware of a physical disability affecting his feet at the age of about 11 and had attended many clinics on this account. He had undergone several orthopaedic operations, including a Steindler operation, a removal of the navicular bone of the right foot, a tenotomy of the extensor tendons of the toes, a subtalar arthrodesis, and a wedge tarsectomy; in 1936 he had had multiple arthrodeses performed on all his toes. During his admission to hospital in 1936 for orthopaedic treatment he was examined neurologically and a diagnosis of Friedreich's disease was made, although this fact was not known at the time of his admission to the Maudsley Hospital in 1938.

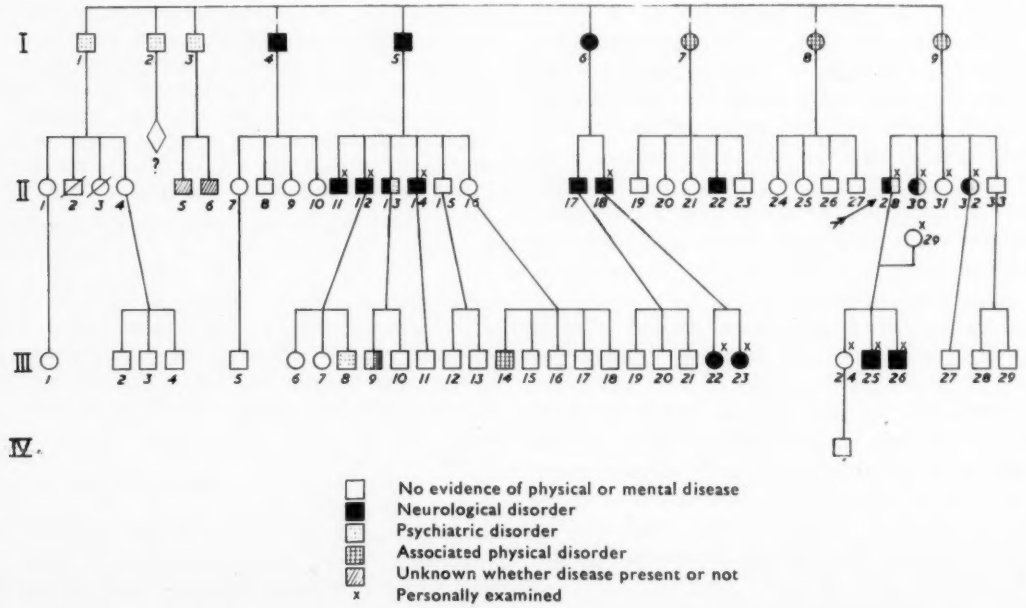
Previous Mental Health.—He was first admitted to the Maudsley Hospital in 1938 when he was referred from Guy's Hospital (Dr. R. D. Gillespie) as a case of schizophrenia. He complained at this time of constant auditory hallucinations; two voices, those of a man and a woman, were with him all the time. He also felt that he was being "controlled" in some indefinable way and he was troubled by constant hissing in his ears. On the subject of his abnormal experiences and ideas the patient was noted to have rambled on indefinitely but in other spheres he was cooperative and rational and at all times retained clear consciousness. He was considered to have been slightly euphoric and to have demonstrated a minimal slurring of speech. In the central nervous system he was noted to have had absent knee and ankle

jerks but no other physical signs were elicited. Bilateral pes cavus, however, was observed at the time. A diagnosis of general paralysis of the insane was mooted until a normal cerebrospinal fluid was obtained on lumbar puncture. Not one of the many doctors who saw him in 1938 questioned the diagnosis of schizophrenia after the result of this investigation.

He was known to have a wife and children at the time but the family history was said to be "negative". After two months in hospital the patient was discharged "cured". There had been a gradual recession of his ideas of influence and reference, and his auditory hallucinations had also disappeared. The only symptom of which he complained at the time of his discharge was a residual hissing in the ears. He was said to have acquired retrospective insight into the abnormal nature of his condition which he regarded as a strange experience and one which he could not explain. He resumed work and remained well for more than a year, but in 1939 was admitted to an observation ward for one week with a recurrence of symptoms. These quickly resolved in hospital and he was discharged home in October, 1939. He remained completely well according to his wife until January, 1953, spending most of the war period in London and standing up well to the inevitable stresses and strains of that time.

Physical State.—On examination, in February, 1953, the patient was a well built, middle-aged man who looked his age. He had a lugubrious expression and very mobile features. Physically he displayed bilateral pes cavus with an equinovarus deformity of both feet which bore the scars of several operations. The remaining physical signs were confined to the central nervous system. Examination of the cranial nerves revealed a bilateral coarse nystagmus most marked on ocular deviation to the right. A slight bilateral ptosis and a slurring dysarthria were also noted. The fundi were normal and no abnormality was detected in the remaining cranial nerves. In the limbs marked bilateral wasting of the musculature below the knees was observed; the intrinsic muscles of both hands were also wasted. There was marked weakness of all wasted muscle groups and the distal musculature of the limbs was weaker than normal. All four limbs were hypotonic. Coordination was impaired in the upper and lower extremities; the gait was ataxic; there was a coarse intention tremor of both arms. Vibration sense was grossly impaired; there was impairment of position sense in the toes; there was relatively slight impairment of pain and touch sensation in the legs up to the knees. All deep tendon reflexes were abolished. The plantar reflexes were equivocal. While in hospital he was examined by two neurologists, one of whom was of the opinion that the patient's clinical picture resembled that of peroneal muscular atrophy rather than of Friedreich's disease, the other favouring the latter diagnosis. The existence of an hereditary neurological disorder stimulated an interest in the possibility of finding other cases and Fig. 1 represents the family pedigree obtained.

Mental State.—Mentally he presented a complex picture. No overt abnormality was apparent in his behaviour in the ward, and at interview he was quiet and cooperative, discussing neutral topics with equanimity. While discussing recent personal and emotionally charged events he became garrulous, displaying short-lived reactions which were often incongruously exaggerated, particularly in the direction of surprise, suspicion, or amusement; he as quickly resumed his even tenor afterwards. He was always in full touch with his surroundings. His mood was mostly euphoric to the point of fatuity. He entertained a number of curious delusional ideas, many of them with a grandiose flavour: with these went constant auditory hallucinations to which he freely gave expression. His attitude to these



abnormal ideas and experiences was at no time paranoid ; on the contrary he appeared to maintain a calm detachment when discussing them. Samples of his talk on admission illustrate these points :

> " I may say that I could see, observe, and separate the spheres (or circular beads of fashion) but I am not in a position to know their names or functions. There was something else to look for which I possess and everyone possesses, the four spheres, the formation : the mind and three others. The mind shares the eyes, the outlook : one for each eye, one higher up in the forehead, keeping clearness of the skull, avoiding pain. Any of them can go adrift, if not tampered with, can be restored normally by the man suffering from these derangements, which are aggravated by the man's intentions . . . I think penetrating rays come through the walls, looking like white steam. They must have enough plates, negatives or positives or what you call them, to supply the world. The same two people I can hear that I heard here last time. I swear by that. A man with a low voice and woman with a sweet voice, with a sweet little voice that can lead you up the garden. The persuasive sort, the film actor, the woman and the man. I call her my Quiz or my Quizzie. Help her day and night ; she must be in close touch with this hospital and they're company for me in my solitude, my friends with their little jokes . . . I am not at all depressed but holy if I may say so. Godly and resigned. I call for assistance or help, give instructions to all environments and functions concerning myself . . ."

By contrast there was no gross abnormality to be detected in his cognitive functions on clinical testing and no obvious thought disorder in the manner in which he answered routine questions. He was quite without insight into his illness and maintained that he was perfectly well at all times.

A number of special investigations were carried out. The blood Wassermann reaction was negative. The C.S.F. was normal. An E.E.G. was within normal limits. An electromyogram was normal. An E.C.G. showed left axis deviation. Dorsal kyphoscoliosis was demonstrated radiologically.

A number of psychological tests were administered. The full-scale Wechsler-Bellevue gave him an I.Q. of 89 (the verbal scale I.Q. was 88 and the performance scale I.Q. 93). A full and careful investigation of his thought disorder was undertaken. The outstanding features of this disorder were considered to be the concreteness, the bizarreness, and the tendency to clang associations. An attempt was made to discriminate between a schizophrenic thought disorder and a thought disorder consequent on brain damage. For this purpose the patient was given the Goldstein-Scherer sorting test, the Rorschach, the Nufferno speed and power test, the Babcock speed test, the U.S.E.S. manual and finger dexterity test, and the M.A.P.S. test : no conclusive evidence of either brain damage or of what is considered to be characteristic of schizophrenic thought disorder was obtained from these test batteries.

Progress.—During his three months in hospital the patient changed little. His general conduct was good, though occasionally he evinced phases of apparent obstinacy which were usually related to some delusional idea, e.g., he refused to shave because

> ". . . I am, according to facial, my figure, my disabilities and my beard which I have let grow from this memory to be like Jesus Christ, who suffered from others as I have in my past. I wish to have His countenance."

He became quieter and refused to discuss his experiences and ideas with anyone except the medical staff. In consequence his wife and family considered him to be well enough to leave hospital and resume work. At the time of his discharge in May, 1953, however, he was still harbouring the same ideas and still experiencing the same hallucinations as at the time of his admission though he discussed them much less freely.

He resumed work at his old job. Seen as an outpatient six months after discharge, he admitted to hearing the same voices and the same hissing in his ears, but was less emphatic about his interpretations of these experiences. In July, 1954 (14 months after his discharge), he was readmitted to an observation ward on account of truculent behaviour and was subsequently sent to a mental hospital under certificate. His mental state was very similar to that described above.

Cases III 25 and **III 26** are the children of the propositus.

Case III 25.—This man, aged 29, was seen and examined. He was noticed to have been suffering from bilateral pes cavus at the age of 3 ; he had difficulty with his feet at the age of 8, when he attended hospital for physiotherapy and exercises until he was 13 years of age. Marked physical disability dates from the age of 17. In 1953 he was seen by an orthopaedic surgeon on account of the deformity of his feet, and he was then referred for a neurological opinion, which was that the case " strongly suggested the diagnosis of the Charcot-Marie-Tooth's type of muscular atrophy ". A radiograph of the spine taken at this time showed ". . . a marked mid-dorsal kyphosis involving most of the vertebrae, presumed Scheuermann's disease ".

On examination this man was well developed physically but showed a kyphoscoliosis and a gross bilateral pes cavus with secondary callosities. In the central nervous system the cranial nerves were normal ; there was no nystagmus and the fundi were healthy. There was wasting and marked paresis of all muscle groups below the knee and some weakness of the thigh muscles. There was also weakness of the intrinsic hand muscles and of the wrist extensors, though there was no apparent wasting of these muscles. The tone and coordination of all muscle groups appeared normal. There was slight impairment of vibration sense, position sense, touch and temperature sensation below the knee. The deep reflexes of the upper extremities were intact ; the ankle jerks were absent and the knee jerks diminished ; plantar reflexes were equivocal.

Case III 26.—This boy, aged 15, was seen and examined. His only previous illness had been at the age of 3 years when he was admitted to hospital, first with a cellulitis and later with acute rheumatism. The hospital notes at that time made no mention of either foot

deformity or central nervous disease. A high arch had been noticed by his parents for the first time one year before he was seen, i.e., at the age of 14.

No obvious mental abnormality was detected at the interview. The patient was a well developed adolescent youth with a dorsal kyphosis and a bilateral pes cavus. No evidence of rheumatic sequelae could be detected in the heart. In the central nervous system the cranial nerves showed no abnormality except for a questionable dysarthria which could not be easily classified; the patient volunteered the information that many people had commented on his "funny" way of talking for some years. There was weakness of the extensor groups of leg muscles; no abnormality could be detected in the musculature of the arms. Muscle tone was normal but he had an ataxic gait with a positive Romberg's sign and an intention tremor of the right arm. There was impairment of position sense in the toes and the vibration sense in the lower extremities was diminished. Both the ankle jerks were absent; the remaining deep tendon jerks were present and equal; the plantar reflexes were equivocal.

Cases II 30 and **II 32** are sisters of the propositus.

Case II 30.—This woman, aged 56, was seen and examined. She was an odd personality, who admitted to being "very nervy". A spinster, she had lived alone for many years meeting hardly anyone except for a few members of her immediate family. She had suffered from foot trouble since childhood and had become increasingly disabled during the past decade. She had a marked bilateral pes cavus. On examination of the central nervous system the cranial nerves showed no abnormality though she spoke with a curious nasal intonation. There was weakness of the extensor muscles of toes and ankles but her most marked motor disability was in the small muscles of the hands, which displayed a considerable degree of atrophy. There was consequent weakness of the intrinsic hand muscles and weakness was also noted in the extensor muscles of the wrists. Tone and coordination of the extremities appeared normal. Position sense in the toes was impaired. Ankle jerks were absent; the knee jerks were depressed; the deep tendon reflexes of the arms appeared normal; the plantar responses were equivocal.

Case II 32.—The second sister, aged 49, was seen and examined. She admitted to having been a "nervous woman" for many years. At the age of 24 she suffered a "nervous breakdown" following her father's death: she was off work for six weeks and stated that she had lost her memory for some days. She had been subject to depressive episodes all her life in which she had displayed self-reproach and had occasionally entertained suicidal thoughts. She considered herself to be free of the familial disease, of the existence of which she was aware. On examination she appeared somewhat despondent but displayed no gross psychiatric abnormality. In the central nervous system no abnormality could be detected other than a pronounced bilateral pes cavus without secondary deformities.

The remaining cases are all more distant maternal relatives of the propositus.

Case I 1.—A male, died, aged 56, in a mental hospital. He was diagnosed as a case of G.P.I. and at necropsy the immediate cause of death was identified as aortic aneurysm. He was also suffering from arteriosclerosis. The Wassermann reaction in the C.S.F. was strongly positive and a paretic Lange curve had been reported shortly before his death. He had been known to be suffering from tabes dorsalis in 1916 and on admission to hospital the positive findings included Argyll Robertson pupils, a tremor of the hands, grandiose delusions, and absent deep tendon and abdominal reflexes.

Case I 2.—This case was a male who died in a mental hospital aged 42. The statutory documents pertaining to this case were examined by permission of the Medical Superintendent of the mental hospital concerned. The patient was admitted under certificate to a mental hospital for the first time in January, 1904, and died there six months later of tuberculous disease of the lungs and intestines which was considered to have been present before admission (information from post-mortem report). His mental illness was said to have begun two months before admission and to have been related possibly to "blindness and an operation to his head"; no further information about either of these circumstances was available. On admission he was considered in the certificate of the medical practitioner to be

> "suffering from delusional insanity, he imagines he can hear his mother talking to him, also other voices, says he has money in the bank, besides a business of his own, he only comes in here to sponge on the rate-payers, if he is kept longer than he wishes he will smash all the windows".

Further imformation was added:

> "He is very noisy, complains of being kept in and would sooner be in hell, threatens to break all the windows and is very abusive towards the other patients. He does not sleep at night and carries on a conversation with imaginary people, and makes use of very obscene language."

Case I 3.—Male, died aged 50+. Known to have been a drunkard for many years.

Case I 4.—Male, died aged 70+. Known to have suffered from trouble with his hands and feet for many years.

Case I 5.—Male, died aged 50+. Known to have suffered from foot deformity and asthma and to have been "round-shouldered" all his life. His son (**Case II 11** says that his own present state is exactly the same as his father's shortly before death.

Case I 6.—Female, died aged 82 in 1950 of "natural bronchial pneumonia, hyperpiesis, and arthritis" (death certificate). According to the evidence of her son she was "nervy" all her life and suffered from bilateral pes cavus during her adult life.

Case I 7.—Female who died of cardiac disease aged 60+.

Case I 8.—Female who died of cardiac trouble aged 70+.

Case I 9.—Female who died of cardiac disease aged 63. She was not afflicted with any abnormality of the central nervous system.

Case II 11.—This man, aged 64, was seen and examined. He was in an advanced stage of the illness when seen but was able to give a clear account of its development. He stated that he first began to "fall" at the age of 8. His foot trouble had become increasingly disabling but not until he was about 39 years of age did he develop trouble with his hands. During the past decade his work had suffered and he was at the time of examination almost crippled with his disabilities. On examination he evinced numerous involuntary movements of the limbs and face and he had an obvious kyphosis of the dorsal spine. He showed bilateral club feet with scars of numerous old operations and multiple callosities on the plantar surfaces. He stated that when he first went to hospital in his 20s he was told that he had "no knee jerks". In the central nervous system he had very small pupils but otherwise the cranial nerves were intact. There was wasting and weakness of the distal musculature of both lower extremities and in addition both the hands showed gross wasting and weakness of the intrinsic muscles and the wrist extensors were also wasted and paretic. There was no tremor of the outstretched arms. Considerable muscular fasciculation was observed in the distal musculature of arms and legs. There was some impairment of the postural and vibration sense of the legs below the knees. No deep reflexes could be obtained in the limbs and the plantar responses were equivocal.

Case II 12.—This man, aged 52, was seen and examined. He was an active working man in spite of a bilateral pes cavus with secondary deformity; the left foot was more severely affected than the right. No abnormality could be detected in either the cranial nerves or in the modalities of power and tone in the limbs. The only sensory abnormality was impaired vibration sensation below the knees in both legs. The deep tendon reflexes were present and equal in all four extremities. This patient also suffered from a left bronchiectasis for which he had been receiving hospital treatment.

Case II 13.—This man, aged 50, was seen, but refused examination. He was regarded by his brothers as an "odd fish" who had little to do with other members of his family. When seen with the psychiatric social worker he was resistive to the point of aggression and refused all blandishments and attempts to persuade him to undergo examination. He admitted however that his feet had been deformed ever since he could remember and had been the cause of many years of misery. It was obvious that he suffered from gross wasting of the intrinsic muscles of the hands. The irritable, peevish, almost paranoid attitude displayed at interview was, according to other informants, characteristic of this man.

Case II 14.—This man, aged 40, was seen and examined. A bilateral pes cavus, more marked on the left than on the right, was the only abnormality detected.

Case II 17.—This case was a male aged 40+, but was not seen. He was stated by a reliable witness (brother) to have suffered from a "tremor of his hands" since childhood. No definite information about his feet was forthcoming.

Case II 18.—A man, aged 42, was seen and examined. He was a physically well developed workman of good average intelligence. He claimed to have been "nervy" all his life. On examination he showed a pronounced dorsal kyphosis. He had marked bilateral pes cavus with no obvious wasting. Nothing abnormal was detected in the cranial nerves. Power and tone of all four limbs were normal but the patient evinced a marked tremor of the outstretched hands and an intention tremor which he said had been present for as long as he could remember. Vibration sense was absent up to the ankle; there were no other sensory abnormalities detected. Knee and ankle jerks were absent; the remaining deep reflexes were present and equal; plantar reflexes were flexor.

Case III 9.—A male, aged 24, was not seen. Information from his father revealed that this boy had been invalided from the army on psychiatric grounds. He also suffered from diabetes mellitus. He had apparently been a difficult person to manage for many years but no further information could be obtained.

Case III 14.—A male, aged 20+, was not seen. He was known to suffer from diabetes mellitus.

Case III 22.—This girl, aged 13, was seen and examined. She had been referred one month before examination to an orthopaedic clinic on account of weakness of the ankles. The orthopaedic report was to the effect that she was suffering from a postural defect which could be remedied by exercises. On examination she proved to have a bilateral pes cavus with absent knee and ankle jerks; the other deep tendon reflexes were present and equal and the plantar reflexes were flexor. No other abnormality was detected in the central nervous system apart from a fine tremor of the outstretched hands and an intention tremor in the upper extremities.

Case III 23.—A girl, aged 10, was seen and examined. This child was apparently asymptomatic but on examination she was shown to have a bilateral pes cavus with absent knee and ankle tendon reflexes. No other abnormality was detected in the central nervous system.

General Commentary on the Family

In summary, reliable clinical information was gathered about 72 members of one family of whom 17 people certainly suffered from some form of inherited neurological disease and a further four from associated physical illnesses. The psychiatric aspects of the case material will be discussed later. There may be merely enumerated at this stage the schizophrenic illness of the propositus, the depressive illness of his sister (Case II 32), the abnormal personalities of another sister, a cousin, and an uncle (Cases II 30, II 13, and I 3), the mental illnesses of the two maternal uncles who died in mental hospitals (Cases I 1 and I 2), and the presumptive psychopathy of his nephew (Case III 9).

It is true, as Hogben (1934) has pointed out, that " Single pedigrees may suggest the lines along which scientific interpretation is to be sought. They cannot in general provide conclusive evidence." Nevertheless, the findings raise a number of genetic, neurological, and psychiatric issues which are still sufficiently obscure to warrant brief discussion.

Discussion

Neurological.—Neurological stigmata were exhibited by both sexes. Twelve out of 28 males and five out of 23 females were affected, the preponderance of males in the family being to some extent responsible for the larger number of male patients recorded.

The earliest symptom of the disorder in either sex was invariably some form of " foot trouble " which made its appearance in childhood. In this connexion Case III 22 is of particular interest, for the patient, a girl aged 13, was seen and examined only a few weeks after her first visit to an orthopaedic clinic with a complaint of "foot trouble"; at the same time her younger sister, aged 10, already displayed evidence of the disease although she was asymptomatic at the time of examination.

Where several collaterals showed neurological symptoms the older members appeared to suffer more severely. This tendency was most clearly illustrated in the case series II 11 to II 16, for the two oldest siblings had been compelled to abandon work in the sixth decade whereas the two youngest were unaffected. The same trend may be witnessed in the case series II 28 to II 33, of which the propositus is the oldest member. It may also be noted that, as far as could be ascertained, life was not appreciably shortened by the disease process among even the most severely crippled ; thus the propositus had had symptoms for at least 42 years, Case II 11 for 56 years, while in no case was it possible to incriminate the disease process as a proximate cause of death.

The form and the severity of the neurological disorder were inconstant in the family. Its least noxious expression was observed in Cases II 14 and II 32, whose bilateral pes cavus constituted the one detectable physical sign. Whereas the lower extremities were invariably and sometimes uniquely affected, the disease process went on to involve the upper extremities of the propositus and of Cases II 11 and II 30. Wasting of the affected musculature was a striking feature in these cases and it is noteworthy that in hospital the propositus was labelled a case of Friedreich's disease by one neurologist but was thought to be suffering from Charcot-Marie-Tooth's disease by another, despite the ataxia, dysarthria, nystagmus, and kyphosis. Further, one of his sons had already been given the latter diagnosis, while the other son showed many of the classical signs of Friedreich's disease. The close relationship existing between Friedreich's disease and peroneal muscular atrophy has been well attested by the several cases and family trees in which both conditions occur (Greenfield, 1911–12 ; Biemond, 1928 ; Spillane, 1940). However, the majority of affected cases in this family demonstrated additional evidence of the more widespread lesions characteristic of the several clinical patterns of Friedreich's disease, e.g., the frequently encountered pes cavus with absent or diminished knee jerks, the motor incoordination (Cases II 18, III 22, III 23), the nystagmus (Case II 28), the dysarthria (Case III 26), and the spinal deformities (Cases III 25 and 26 and II 11 and 18). Of the better recognized physical associations of Friedreich's disease diabetes mellitus was reported in Cases III 9 and III 14 and heart disease was known to have afflicted Cases I 7, I 8, and I 9.

This prolixity of clinical variants can be best elucidated by reference to the intermediate and abortive forms of the heredo-familial ataxias which, as Roth has shown, require a genetic framework for their full understanding (Roth, 1948). The genetics of these disorders are complex and have not yet been worked out in their entirety. The necessity for postulating more than one Mendelian factor to account satisfactorily for the mode of transmission of Friedreich's ataxia, about which most is known, was early suggested by Brain (1925). From the evidence of her pooled case material Bell was enabled to demonstrate the close genetic links between Friedreich's disease, spastic ataxia, and spastic paraplegia, each of which claimed a dominant and a recessive type of inheritance. It appears probable that a sex-linked variant of all these conditions also occurs, and Haldane has speculated on the possibility of the existence of allelomorphic subdivisions existing within the three clinical conditions (Haldane, 1941).

It may be observed from the present family tree that the neurological abnormality was inherited as an irregular, autosomal dominant. This form of transmission is most unusual in recorded pedigrees of Friedreich's disease. Thus in Sjögren's experience all patients with Friedreich's disease exhibited a recessive form of inheritance. Bell and Carmichael comment specifically on their failure to meet with a single case of Friedreich's disease " . . . which was demonstrably of dominant genetic type " out of the 46 families they examined, and they went on to state that such cases were rare in the pooled material. It seems reasonable to suggest that the

number of clinical differences discerned is directly related to the less common but more pleiomorphic dominant gene ; and it is of interest that the families adduced by Spillane and by Roth as a basis for discussion of the intermediate forms of hereditary ataxia all displayed the dominant mode of transmission. The evidence to be derived from the present family thus further supports the case made by these authors for the discarding of rigid clinical syndromes within the group of disorders, and illustrates Kinnier Wilson's comment that " . . . by easy steps the Friedreich syndrome may move toward muscular dystrophies, spinal amyotrophies, spinal paraplegias, cerebellar or cerebral states " (Kinnier Wilson, 1940).

Psychiatric.—The mental changes associated with the heredo-familial ataxias, and in particular with Friedreich's disease, have received much less attention than the physical manifestations of these disorders. Most observations by neurologists have been focused on the impairment of cognitive ability to the neglect of the more complex mental functions, which are characteristically dismissed by Kinnier Wilson as " . . . instances of feeble-mindedness, mental debility, or worse ". The co-existence of psychotic illnesses with Friedreich's disease has for long been recognized by Continental workers, however, and many different abnormal mental states have been described, usually in isolated cases. After fully reviewing the relevant literature Davies' conclusion was that " . . . the relationship of the mental and neurological disorders is more fundamental than fortuitous ", although the nature of this relationship remains complex and obscure (Davies, 1947).

In the family under discussion several examples of mental abnormality were noted, most of them with but some without concomitant neurological disease. Of the former group the propositus presented a clear picture of schizophrenia, a diagnosis which had been made by a number of competent observers unaware of the nature of the neurological condition. The sister of the propositus, whose only neurological signs were those of a pes cavus and absent ankle jerks, suffered mild, recurrent depressive illnesses. Abnormal personality traits were observed in Cases II 13 and II 30 and their presence was corroborated by other witnesses ; both patients were suffering from an advanced degree of neurological disability but not more than Cases II 11 and III 12, which showed no evidence of mental disturbance. These cases were personally seen and examined. The clearly described alcoholic and psychopathic features of Cases I 3 and III 9 indicated abnormal personality traits without neurological disease. The mental symptoms of Case I 1 must be regarded as dependent on his G.P.I., though it may be noted that he had previously been thought to suffer from tabes dorsalis, a diagnosis which has often been confused with that of Friedreich's disease. Lastly, the interesting mental illness of Case I 2, characterized by prominent delusional ideas and auditory hallucinations, appears to have been unassociated with neurological signs or symptoms.

It is not proposed here to discuss at length the general issue of the association between Friedreich's disease and the variegated forms of mental abnormality demonstrated by the family under consideration. Insufficient knowledge is available about the background and genesis of many of the psychiatric states observed and recorded. Attention is more profitably focused on the propositus, about whose schizophrenic illness extensive data were acquired.

The majority of recorded psychoses accompanying Friedreich's disease are of paranoid or frankly schizophrenic type, often with hallucinations, and the coincidence has provoked much interest in the past. The combination was striking enough to lead Kleist 30 years ago to speculate on the possibility of schizophrenia being a form of system-degeneration analogous to that postulated for the heredo-familial disorders (Kleist, 1923). At about the same time Lewis (1925) was led by similar considerations to regard the schizophrenic constitution as " . . . an heredo-degeneration whose localization was not at the higher neurogenic levels, but consisted of a defective factor outside the neuroectoderm with the primary focus located in those primitive cells the later differentiation of which produces the mesodermal and entodermal structures ". Conversely, in the opinion of de Smedt and others, the psychiatric and neurological conditions are genetically distinct even when clinically associated, a point of view which has been adopted by several other workers in the field (Smedt, Wulf, Dyckmans, and van Bogaert, 1937). An intermediate view is discussed by Birkmayer and Lenz in relation to their patients who suffered from both disorders and came from a family with mental illness on the paternal side and neurological disease on the maternal side : they admit the possibility of a mutual reinforcement of genetic factors in a non-Mendelian fashion, bringing about a more pronounced clinical picture in predisposed cases (Birkmayer and Lenz, 1939). Unfortunately for the testing of this latter hypothesis, the family history of the propositus was obtainable in the present instance on only the maternal side, though no knowledge of paternal illness was vouchsafed by the numerous informants. There may, therefore, be more genetic significance in the mental illness recorded of the patient's

maternal uncle (Case I 2) which is compatible with a schizophrenic reaction. It remains unclear why the propositus alone exhibited the admixture of schizophrenic and neurological symptoms.

The most recent attempt to explain the association between Friedreich's disease and the psychoses encountered with it has been propounded by Bleuler and Walder (1946). According to them, the mental state in Friedreich's disease exemplifies the so-called psycho-organic syndrome (Bleuler, 1951), and is closely akin to that witnessed in the psychoses associated with epilepsy which the authors consider to be due to diffuse, slowly developing brain damage; they point to the mild dementia, the egocentricity, the euphoric mood, and the delusional ideas and hallucinations with a religious content as evidence of the symptoms common to both conditions. Their view has been upheld by several Continental workers (Blöchlinger, 1946; Schneider, 1946; Knoepfel and Macken, 1947) and it is worth noting that only one case history was included in their original paper, that of a 53-year-old woman whose neurological symptoms dated from childhood and had become incapacitating by the age of 33. Her mental state was thought to be indistinguishable from that seen in a psychosis associated with epilepsy. As a single case the propositus bears close comparison to Bleuler's patient in respect of age, the early onset of neurological symptoms, and the relatively late appearance of very similar mental symptoms which included delusional ideas and hallucinatory experiences with a religious content. However, detailed clinical and psychological examination (the tests employed being far more refined than those used by Bleuler) failed to show any evidence of brain damage. Further, the E.E.G. yielded no support for the diagnosis of epilepsy.

The whole concept of the Friedreich psychosis as an example of the psycho-organic syndrome has been assailed by Davies principally on the ground that there is no satisfactory pathological evidence of diffuse cerebral changes in Friedreich's disease (Davies, 1949). The suggestive features of individual cases he accounts for in terms of the uncommon but established association of epilepsy with Friedreich's ataxia along with the secondary effects of chronic invalidism. The case history of the propositus further illustrates the difficulty imposed by over-simplification, since epilepsy and dementia can be definitely excluded in spite of a clinical picture which would have qualified in most respects for inclusion among the cases chosen to exemplify Bleuler's syndrome. The existence of the several other and variegated psychiatric conditions described in the family also poses questions which cannot be answered in terms of the psycho-organic hypothesis alone.

The psychiatric disorders associated with Friedreich's disease would seem, therefore, to demand a broader approach for their elucidation. The known genetic factors influencing the transmission of the heredo-familial diseases constitute an obvious field of enquiry, complementary to the clinical observation of individual cases. However, as the present pedigree clearly indicates, it will be necessary for this purpose to accumulate and study both family pedigrees and individual cases which have been as well investigated from the psychiatric as from the neurological points of view.

Summary

A family has been described in which 17 members exhibited various forms of heredo-familial ataxia. The clinical and genetic aspects of the neurological disorders have been discussed.

In addition, the propositus was suffering from a schizophrenic illness and six more members were traced with psychiatric histories of different types.

The possible relationships between heredo-familial ataxia and schizophrenia have been discussed. Further doubt has been cast on the concept of the psycho-organic syndrome as applied to this association.

I should like to acknowledge the invaluable assistance afforded by the psychiatric social worker, Mr. Edgar Myers, without whose diligence and pertinacity many members of the family tree could not have been traced. I am also indebted to Dr. Eliot Slater for his suggestions and advice.

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LOCALIZED ENLARGEMENT OF THE SPINAL CANAL IN THE ABSENCE OF TUMOUR: A CONGENITAL ABNORMALITY

BY

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When Elsberg and Dyke (1934), having studied a series of antero-posterior radiographs of normal spines, reported the range of normal variation in the distance separating the inner borders of the vertebral pedicles, they provided information which has required no important modification since that time. They pointed out that an unusual and localized increase in the distance between the pedicles was to be seen in the presence of intraspinal tumours that were both intrathecal and extrathecal. They wrote (p. 392) that after excluding recent or old fractures of the spine " the enlargement of the vertebral canal described in this paper was found exclusively in expanding lesions within the vertebral canal, and the increase in size always corresponded to the position of the neoplasm ". They observed that only further experience would show whether " enlargement of the interpedicular space " occurred except with an expanding lesion. Elsberg, Dyke, and Brewer (1934) made it clear that an " expanding lesion " was not necessarily a neoplasm, by describing four adolescent patients who had upper thoracic extradural cysts and showed eroded vertebral pedicles. Earl Walker (1944) recorded the findings in four cases where the neurological signs and a study of the pedicles indicated intraspinal neoplasm, but in all four patients a congenital anomaly of the cord was present. In only one case was there any clinical suggestion of spinal cord compression and in two of his cases (p. 581) " there was much more room in the subarachnoid space than usual ". The present writer has been unable to trace published reports recording dilatation of the vertebral canal, apparently similar to that described by Earl Walker, but unassociated with abnormalities of the spinal cord. This publication reports two such cases and, by contrast, a third case in which a somewhat similar vertebral appearance was associated with an extradural cyst, without signs of cord compression.

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Case Reports

Case 1.—A woman, aged 22 (R.I. 180511/53), at the age of 11 years was said to have outgrown her strength and developed a slight scoliosis. Remedial exercises were performed with satisfactory results. Five years before admission she began training in a dancing college and discovered that after a day of mental and physical exercise she would find herself very tired. Quite frequently she would wake in the morning with a stiff back. Fifteen months before admission, at a time when she was unusually busy, she began to get an occasional " red hot feeling " on each side of the lower thoracic spine. Because of this complaint she came under medical observation and, subsequently, radiographs of her back were taken. At no time did she have any neurological symptoms, and examination at the time of her admission disclosed no neurological abnormalities. The movements of the spine were full and painless, straight leg raising was unimpaired, and the power, tone, reflexes, and sensation in the legs were entirely normal. The only abnormality on clinical examination was that the spine of the eleventh thoracic vertebra was less prominent than were its neighbours. The radiographs of the spine in the lateral view confirmed that the spine of the eleventh thoracic vertebra (T.11) was rudimentary and also showed stunting of the spine of the twelfth thoracic vertebra. The lateral view showed that the antero-posterior diameter of the spinal canal was increased opposite the bodies of T.12 and the first lumbar vertebra (L.1), suggesting an enlargement of the spinal canal as by an expanding lesion. The antero-posterior view showed a fusion defect in the lamina of T.11 and an unusually slight shadow for the spine of T.12. There was, in addition, widening of the vertebral canal with narrowing of the pedicles of T.12 and L.1 (Fig. 1). With the exception of T.12 and L.1 the measurements between the pedicles throughout this patient's spine approached the lower limit of normal as given by Elsberg and Dyke (1934). The interpedicular distance at T.12 and L.1 increased sharply to the upper limits of normal. (The measurements of the interpedicular distance were: T.10 = 18 mm., T.11 = 20 mm., T.12 = 25 mm., L.1 = 27 mm., L.2 = 25 mm., L.3 = 24 mm., L.4 = 25 mm.) The figures published by Elsberg and Dyke (1934) are reproduced in the Table.

FIG. 1a

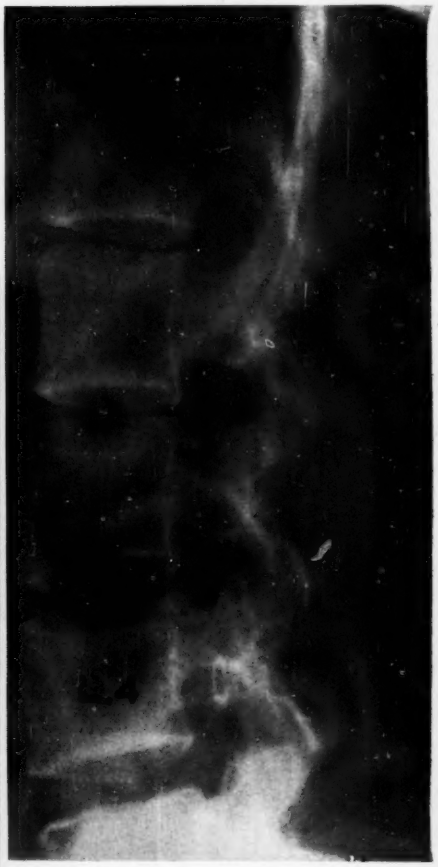

FIG. 1b

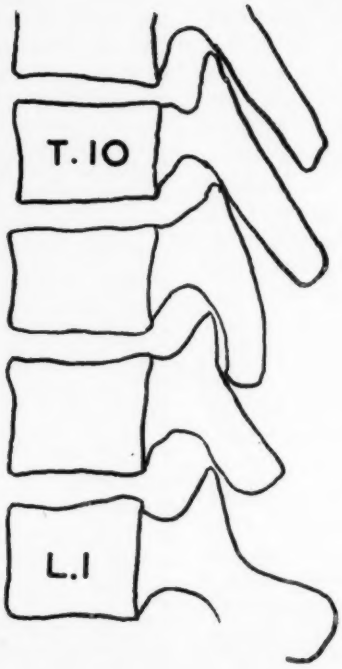

FIG. 1c

FIG. 2

FIG. 1.—Case 1: radiographs of the thoracolumbar junction.

a. Antero-posterior view showing incomplete fusion of the spine of T.11 (arrow), also poorly defined spine of T.12, and thinned pedicles T.12 and L.1.
b. Lateral view, in which is seen the antero-posterior enlargement of the spinal canal opposite the body of L.1 compared, for example, with L.4.
c. Tracing of the lateral view to show defective vertebral spine of T.11 and T.12.

FIG. 2.—Case 2: Radiographs of the thoracolumbar junction in the antero-posterior view to show abnormality of the pedicles. The appearance is compatible with erosion by an expanding lesion.

TABLE

INTERPEDICULAR DISTANCES AS PUBLISHED BY ELSBERG AND DYKE (1934)

Vertebra	Usual Size of Interpedicular Space (mm.)	Extreme Sizes (mm.)	
		Lowest	Highest
C.4	27–32	25	34
5	28–32	25	33
6	27–32	25	34
7	27–31	22	33
T.1	23–27	21	30
2	19–23	18	25
3	18–22	17	22
4	17–20	15	20
5	17–20	15	21
6	16–20	15	21
7	16–20	14	21
8	17–20	13	22
9	17–22	15	22
10	18–21	14	23
11	19–23	16	27
12	21–26	18	30
L.1	23–28	20	33
2	24–29	22	33
3	25–30	22	35
4	25–31	23	35
5	28–33	24	39

By "usual size" Elsberg and Dyke meant "the range in from 80 to 95% of the cases".
The "extremes" were the lowest and highest figures obtained in the measurements of 200 normal spines.
(Their paper showed that the measurements observed were scarcely affected when the tube-film distance varied between 30 in. and 41 in.)

These findings made a lumbar puncture desirable. The initial pressure was 130 mm. of water, there was a slightly sluggish rise on jugular compression, but a normal fall. The fluid contained 40 mg. protein/100 ml., no red blood cells, and four lymphocytes per c.mm.

The conclusion was drawn from these findings that the spinal canal was enlarged and that in view of the evidence of malformation of the vertebral spines an intraspinal dermoid or lipoma might be present. However, the fact that there were no neurological abnormalities and no manometric block on spinal puncture indicated that compression of the cord had not occurred. Largely at the insistence of the patient and her family, the abnormal region was explored. At operation the spines of T.11 and T.12 were found to be rudimentary, though the supraspinous ligaments and the muscle attachments were well developed. The laminae were removed and the normal amount of extrathecal fat was encountered in the vertebral canal. The unopened dura had a bluish tinge, as though a big cyst might be within, but after the dura was incised it could be seen that the vertebral canal was greatly distended and the spinal cord and its roots appeared normal, as did the leptomeninges. There was no obstruction above or below this level, for a catheter passed freely both upwards and downwards.

Post-operatively the patient did well and 18 months after the operation was symptom free.

Case 2.—A woman, aged 18 (R.I. 198481/54), four years before admission began to have low back pain and pain at the lateral aspect of the left calf which was without preceding trauma and of gradual onset. The pain had many of the characteristics of sciatica caused by a prolapsed intervertebral disc and it was with this possibility in mind that she first came under medical care. She was admitted to hospital after conservative treatment had failed to relieve her. At the time of admission the only abnormalities on examination were very slight weakness at the left ankle which may have been partly occasioned by pain, and a little blunting of sensation to pin-prick on the outer aspect of the left lower leg. The back movements, though initially good, were later limited, as was straight leg raising on the left. Further radiographs were taken and these disclosed a dilatation of the spinal canal, as indicated by scalloping of the posterior aspect of the vertebral bodies, especially the first lumbar vertebra, and by an increase in the interpedicular distance with narrowing of the pedicles (Fig. 2). The distances between the pedicles from T.7 to T.11 were at the extreme upper limit of normal given by Elsberg and Dyke (1934), and, although the pedicles of T.12, L.1, and L.2 had a more abnormal form, they were not separated by such an unusually great distance. (The measurements were : T.7 = 22 mm., T.8 = 22 mm., T.9 = 23 mm., T.10 = 24 mm., T.11 = 25 mm., T.12 = 27 mm., L.1 = 29 mm., L.2 = 29 mm., L.3 = 28 mm., L.4 = 28 mm., L.5 = 30 mm.) There were in addition some minor congenital abnormalities of the vertebrae. Because of the expanded vertebral canal a spinal cord tumour was suspected and a lumbar puncture showed an initial pressure of 135 mm. of water with normal responses to jugular compression. The protein level was 40 mg./100 ml. and there were no cells. A myelogram showed no abnormality at the lumbo-dorsal junction and equivocal changes only at the L.4–5 disc interspace. Because the symptoms remained severe an exploration of the disc spaces at L.4–5 and L.5–S.1 on the left hand side was carried out. No abnormalities were detected. The opportunity provided by this operation was taken to explore the upper lumbar spine, and the spine and lamina of the second lumbar vertebra were removed. The bone of the lamina was unduly thick and hard. Microscopical examination of it, however, disclosed no significant abnormality. The spinal canal was seen to be enlarged, and after opening the dura it was possible to be absolutely satisfied that the cord and the spinal nerve roots were normal. Post-operatively the patient was unexpectedly relieved of her leg pain and when seen three months later was symptom free and had a full range of movements in her back.

Discussion

Enlargement of the spinal canal with congenital abnormalities of the cord is not particularly uncommon. Herren and Edwards (1940), for example, drew attention to dilatation of the spinal canal associated with duplication of the spinal cord, and the literature on diastemato-myelia contains several accounts of dilatation of the spinal canal. Earl Walker (1944) recorded abnormal enlargement of the spinal canal, apparently similar in type to that noted here, but all his patients had abnormalities of the spinal cord with resulting neurological disabilities. The two cases reported here differed from Walker's in another minor respect, for his

patients all had abnormally short vertebral spines and the laminae were wider and thinner than normal. Although in Case 1 the spine of T.11 was short, it was not associated with a notably deformed lamina and in Case 2 the lamina appeared thicker than usual. Walker suggested that the enlargement of the spinal canal in his cases had occurred in the development of the individual. He was able to say this because the associated abnormality of the cord provided unequivocal evidence of abnormal development in that region, and the excessive size of the spinal canal clearly resulted from maldevelopment and not from pressure erosion. Among the published cases of intrathoracic meningocele enlargement of the spinal cord and erosion of some of the vertebral pedicles are, in many of the reports, either described or may be inferred to have occurred ; scalloping of the posterior aspects of the vertebral bodies was a feature of some cases. These changes were well illustrated by Kessel (1951) who also referred to the previous literature. In addition Kessel quoted and illustrated a personal communication from Bull (1950) which is of considerable interest. The report concerned a 37-year-old woman with neurofibromatosis who had gross enlargement of the vertebral canal and, at necropsy (death was due to cerebral tumour), the posterior aspects of the vertebral bodies T.12–L.3 were seen to be hollowed out. The " distended theca " bulged through the large intervertebral foramina. Bull's patient may have shown a more advanced example of the abnormality described by the present writer. (See also the case reported by Mendelsohn and Kay in 1949.)

A congenital abnormality of a single vertebral pedicle sometimes occurs. In the example recorded by Steinbach, Boldrey, and Sooy (1952) one cervical pedicle appeared to be eroded, but there were no abnormal neurological findings and a surgical exploration revealed no tumour. These authors suggested that future cases might be correctly diagnosed because of the compensatory structural changes in the bone.

Case 1 reported here came under observation because of mild back pain and Case 2 had no symptoms referable to the upper lumbar spine. In neither case were there any significant neurological abnormalities, the slight changes in Case 2 being presumably referable to another pathological process. The experience of these two cases shows that when the relevant symptoms are mild, and when there are no neurological abnormalities and the lumbar puncture findings are normal, then dilatation of the spinal canal, especially when associated with congenital abnormalities of the affected vertebrae, may be regarded as a benign condition and of no serious significance. However, when pain is a prominent symptom, enlargement of the upper lumbar spinal canal associated with normal neurological findings and a normal cerebrospinal fluid may have an alternative origin. The following case which I saw at operation illustrates this. (The patient had been referred to Professor Sir Geoffrey Jefferson by Mr. D. Ll. Griffiths and I am indebted to them for permission to record these findings.)

Case 3.—A woman, aged 63, four months before operation had influenza and felt extremely and unusually ill. She shortly developed a very unpleasant upper lumbar backache which " gripped " her and from which pain, at times, spread either into the hips or down the backs of both legs to the knees. The pain continued and became unbearable, in spite of very large doses of aspirin, and admission to hospital was arranged. On examination spasm of the erector spinae muscles was severe and, although she could stand out of bed, forward flexion was impossible. Neurological examination was entirely normal. A lumbar puncture was normal with a protein level of 35 mg./100 ml. and one white cell per c.mm.

The radiographs showed considerable erosion of the pedicles of T.12, L.1, and L.2 with enlargement of the intervertebral foramina. There was no scalloping of the posterior aspects of the bodies of the affected vertebrae, but the antero-posterior measurement of the spinal canal was greatly increased because the laminae were thinned and were lying exceptionally far posteriorly (Fig. 3). At operation the affected laminae were less deeply situated than is normal and the spinous processes were unusually short. The bone of the laminae of L.1 and of L.2 was in parts little thicker than an egg-shell. On removing the bone a cyst cavity which extended from T.12 to L.3 (inclusive) was disclosed. Fluid from the cyst contained protein, 30 mg./100 ml., sugar, 55 mg./100 ml., and chlorides, 700 mg./100 ml. The cyst cavity was roughly cigar shaped and lay dorsal to the spinal canal ; its floor was intimately fused with an altered and semi-transparent dura mater and no extradural fat was seen. The dorsal wall of the cavity was excised, and microscopical section showed it to consist of collagen with an incomplete layer of endothelial cells. No communication with the subarachnoid space could be demonstrated. The dura surrounding the spinal cord was not opened.

This lesion presumably should be classified as an extradural cyst, though it differed in several important respects from those described by Elsberg and others (1934).

Summary

Two cases are described of dilatation of the spinal canal at the thoraco-lumbar junction with an *x*-ray picture simulating an expanding lesion. In both of them full investigations, including operation, disclosed a normal cord lying in an enlarged sub-

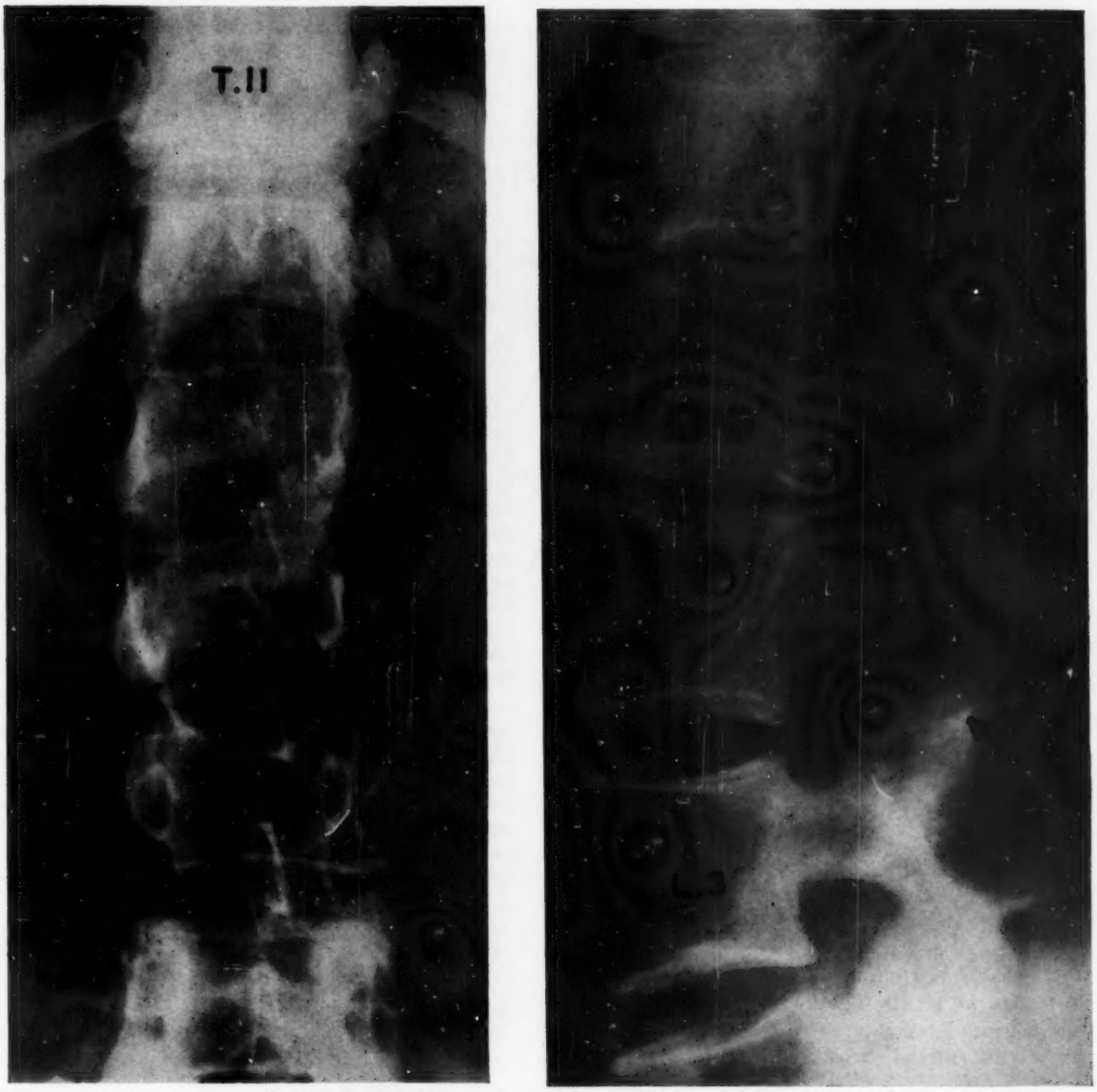

FIG. 3.—Case 3 : Radiographs of the thoraco-lumbar junction.

a. Antero-posterior view showing widening of the canal and erosion of the pedicles. Arrows indicate the well defined lower margin of extreme expansion of the lamina of L.2 (cf. lateral view).

b. Lateral view, in which the canal is seen greatly widened with pedicles thinned and intervertebral canals consequently enlarged. The arrow indicates the lower margin of extreme expansion of lamina of L.2.

arachnoid space. The significance of these findings is briefly discussed and the findings are contrasted with those in an unusual case of extradural cyst.

I am grateful to Mr. Joe Pennybacker for advice in the preparation of this paper and for permission to record Cases 1 and 2. Case 2 was referred by Mr. J. C. Agerholm.

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AN ELECTRODE HOLDER FOR DIRECT ENCEPHALOGRAPHY WITH ITS OWN STERILIZING CABINET

BY

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Direct recording from the human brain has been outgrowing purely electrophysiological interest. Several technical problems had, however, to be solved in order to offer the neurosurgeon a reliable and flexible method of rapid investigation of the electrical activity of the brain exposed during operations.

One of the important tools is the holder for the electrodes in corticography. Three types of electrode holder have been described (Jasper, 1951 ; Marshall, 1949 ; Grass, quoted by Schwab, 1951) although it is probable that other models not described in the available literature are also in use.

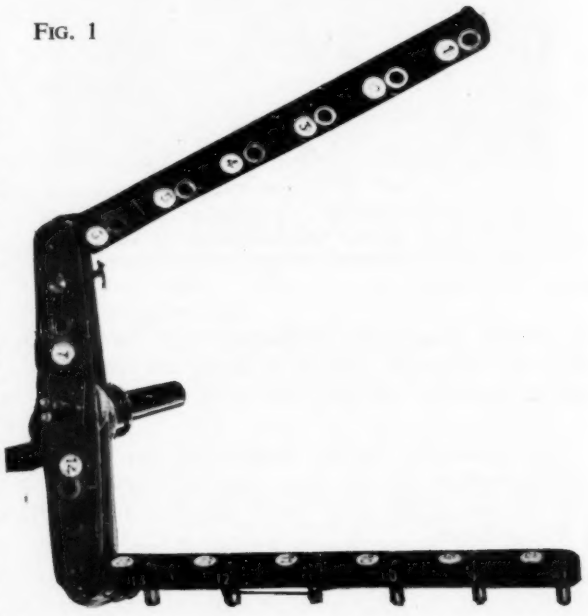
The electrode holder described below has some advantages over previously described models. It was designed to meet the following requirements : (1) Lightness and appropriate mobility ; (2) reliability of contacts ; (3) ease of replacement and interchangeability of various kinds of electrodes ; (4) stable fixation to the skull while allowing immediate removal in case of emergency ; (5) sterilization in formalin vapour ; (6) possibility of stimulating the brain while recording ; (7) possibility of taking photographs of the brain with electrodes in position without obstruction to the view. In collaboration with Mr. M. A. Falconer, the present model, after several trials, has been found satisfactory for routine use since 1953. This model can be built in any small workshop using materials with a fusion point near or below autoclave temperatures. This offers considerable constructional advantages.

The holder (Fig. 1) consists of a central portion or body and two lateral portions or arms. The ball-and-socket connecting base of a de Martel retractor is fixed to the central portion or body, permitting mobility of the holder in various planes and its subsequent fixation at various angles. The base of the de Martel retractor is slipped on to its square peg which has been previously fitted into a drill hole in an appropriate part of the skull. This arrangement is particularly useful as it disposes of the skull clamping device used in all the other models ; should the brain herniate suddenly through the bone flap the peg does not cause interference, while the holder can be immediately lifted or removed. The body of the holder, which is 3 in. long, is made of two parallel plates of " tufnol " ($\frac{1}{8}$ in. thick). At each end these plates clamp a ball ($\frac{7}{16}$ in. diameter). A tension screw allows stability and good friction on each ball on which the arms are fixed.

Each lateral portion or arm can be swivelled to any position about the ball joint which attaches it to the body. This feature proved particularly useful when exploring a large area, for each arm would be adequately and independently orientated. Each arm is made of " bakelite " ($\frac{1}{4}$ in. thick) and is 5 in. long. Six sockets for electrode mounts are placed in each arm and two in the body (a total of 14).

Each electrode mount (Fig. 2 A) is formed by two OZ plugs (A1 and A2). The top of A1 is suitably cross drilled to act as a socket for A2, which is also cross drilled to house (soldered) a short piece of brass tubing (0·052 in. lumen). A small wire spring inside the brass tubing ensures good contact with the rigid part A3 (stainless steel tubing) of the actual electrode. Such an arrangement allows to-and-fro movements of the

FIG. 1



electrode as well as its rotation in both vertical and horizontal planes while the slight friction avoids undesirable looseness.

From the sockets the leads (7·009 PVC covered) recess in the underside of each arm and join with the leads from the other arm and from the body to form a cable. The cable is shielded all its length with braiding (insulated from the metallic parts of the holder). An additional rubber tubing covers the whole cable form. Each lead at the end of the cable (8 ft. long) is connected by means of individually numbered plugs to the input box extension (clamped under the operating table) of the E.E.G. apparatus.

Each electrode (Fig. 2, A3) is a silver-silver chloride bare ball on a silver lead soldered to a length of stainless steel tube (0·048 in. diameter, 2½ in. long) which slides in the electrode mount. The silver lead (32 S.W.G. four lengths 5-8-10-12 cm.) has sufficient spring in it to maintain contact on the brain. In addition flexible insulated silver leads for recording from non-exposed surfaces or cavities and light needle electrodes for depth recording are included in the equipment. At the distal end of the patient these special electrodes are soldered to single plugs (Fig. 2B) which fit in the sockets. All the electrodes therefore are interchangeable.

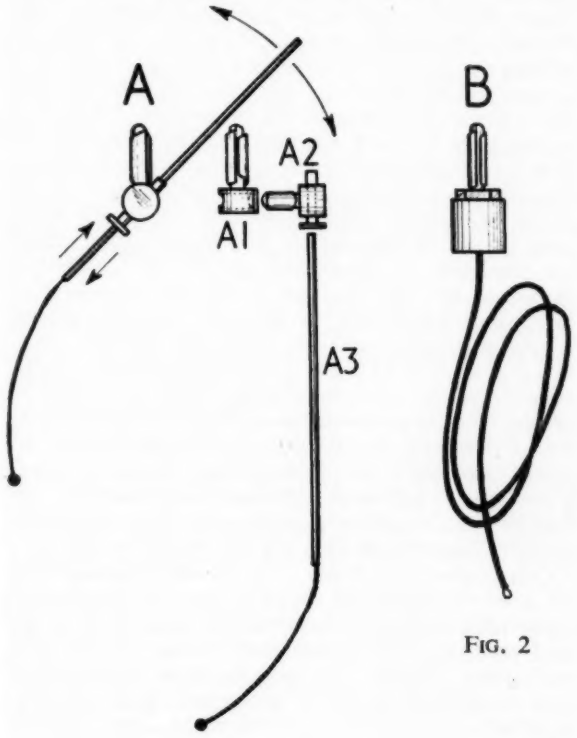


FIG. 2

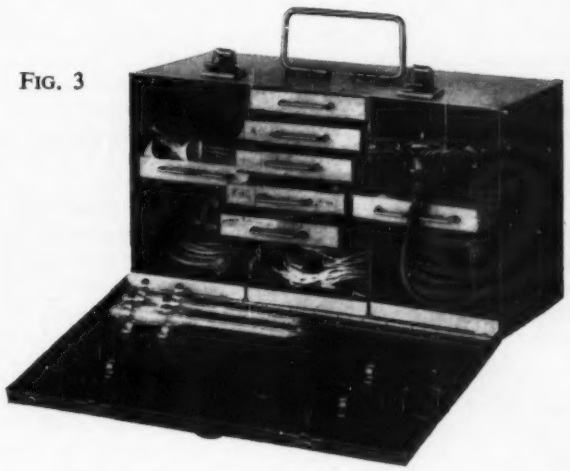


FIG. 3

Stimulation of the brain may be performed either directly or through the recording electrodes by applying the terminals to appropriate contacts near the sockets.

A special cabinet (Fig. 3) was built for keeping and sterilizing two electrode holders, the various electrodes, and the stimulating electrodes and their cables. The five drawers in the central portion contain electrodes of various lengths and types. One electrode holder is placed in each side drawer, the right hand one of Fig. 3 being that described above. Each cable is rolled in the recess below each lateral drawer and in the middle there is a cable for the stimulator electrodes. All drawers are perforated to permit the circulation of vapour from formalin tablets scattered around under gauze and at the bottom of the cabinet. The cabinet is closed and sealed with adhesive tape. After a minimum of 24 hours the apparatus is sterilized and ready thereafter for use in the operating theatre. Following each operation the holder, all the electrodes, and the cables and terminal plugs are carefully checked before going back into the sterilizing cabinet.

Our thanks are due to Mr. Murray A. Falconer, Dr. Denis Hill, Mr. P. St. John-Loe, Mr. D. Nelligan, and Mr. J. Theobald for their suggestions, help, and cooperation, and to the Department of Medical Illustrations, Guy's Hospital, for the photographs and drawings.

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BOOK REVIEWS

Brain Mechanisms and Consciousness. A Symposium. Edited for The Council for International Organisations of Medical Sciences established under the joint auspices of U.N.E.S.C.O. and W.H.O. by J. E, Delafresnaye. (Pp. xv + 556 ; illustrated. 42*s*.) Oxford : Blackwell Scientific Publications. 1954.

This symposium includes 18 prepared contributions each followed by a condensed discussion, together with a final general discussion on the subject as a whole. Greater emphasis has been laid on prepared papers than was the case with other symposia previously published, and the result is to make the volume heavier to read but possibly more valuable in the amount of reliable information that it conveys. The authors include many of the best known contributors to the neurophysiological field pertaining to the diffuse projection system which has received so much attention in recent years, e.g., Morison, Lashley, Jasper, Magoun, Bremer, Hess, Moruzzi, and others. The British contributors are Adrian and Grey Walter.

The main argument is well propounded by Fessard who suggests that the phenomena of consciousness are those of an " experienced integration " of nerve impulses. The three possible loci for such a function are the brain as a whole, the cortex as a whole, and lastly one specific part of the brain which can receive abstracted information from other parts of the brain which participate in its passage only in the form of unconscious operations. At this point Fessard goes to the reticular structures of the diencephalon and brain-stem to find one possible integrating structure. Such a descent finds favour with Penfield, who has long pressed for a "centrencephalon" on philosophical grounds. Reasons cited for the recourse to the brain-stem, which Penfield calls the *highest* centre, include the work of Magoun showing that the reticulum of the midbrain is necessary for consciousness, and that of Lashley which showed that isolation of portions of sensory or sensorimotor cortex from all but centrally passing fibres did not destroy perceptive or learning abilities in animals. These authors (Magoun and Lashley) regard this interpretation of their own work with considerable caution, and even, it seems, almost with embarrassment. Indeed, Lashley states flatly that the reticular substance may act as an activating agent or "pace setter" for the cerebral cortex, but this is certainly all that can be claimed for it at present.

One weakness in the meeting is in the paucity of references to temperamental disturbances in experimental animals. One of the few studies cited is that of MacLean, whose suggestion of a specifically afferented hippocampus as part of his " visceral brain " has already been subjected to considerable criticism in the literature. If, as seems likely, temporal lobe cortex is involved in affective states, and if the hippocampus and fornix, or other diencephalic connexions, are capable of influencing the rest of the cortex as Lashley suggests as a " pace setter ", then the evidence presented in this volume would seem to point towards the associative area in the temporo-parietal lobe of the dominant hemisphere as fulfilling most of the criteria demanded by Fessard. The implication seems to be that by such means the abstracting " secondary integrative level " of, say, the frontal lobes could be switched in and out like the frequency analyzers of the E.E.G. machine, with emotional considerations " controlling the switch ". These ideas are not new. Herrick suggested something of the sort for the function of the rhinencephalon in 1933.

Whether all this be reasonable surmise or not, the reader will almost certainly be encouraged to formulate some synthesis for himself after reading this symposium. Other chapters include one on anaesthesia by Mary Brazier which shows how profound is our ignorance of the essential mode of action of the commonest drugs.

Moruzzi describes how cerebellar stimulation affects the reticular substance of the brain-stem, but there is considerable doubt in the minds of the others whether it was the ascending or descending reticular substance. Final doubt is also left about the upward prolongation of the ascending reticular substance. Similar effects were found on stimulation of subthalamic structures, but the diffuse non-specific projection through the thalamus, although it produced widespread changes in the cortical E.E.G. patterns, might not arouse the animal. Elkes and Bradley in this country have found a similar dissociation following the use of certain drugs. Indeed Hess claims that stimulation of the thalamic non-specific projection system actually caused sleep which lasted for a long time after the stimulus ceased. However he was using " stimulus " waves lasting 1/80 sec. (12·5 m.sec.) 8 per second, and in the opinion of some workers, this duration and frequency may produce effects opposite to those of stimulation.

One further point is left in doubt. It would seem that some of the synchrony between the two hemispheres occurs independently of the known commissures, and may be mediated through brain-stem structures. How this occurs remains a mystery, though it seems unlikely that it represents any form of point-to-point projection such as is mediated through the corpus callosum, and possibly the anterior commissure.

Grey Walter describes his toposcope and his conditioned reflex analogue, while Adrian's chapter on the physiological basis of olfactory perception is a model of lucidity.

This book should be read by everyone interested in the brain, and it should be read soon before the ever-

increasing volume of new work on these subjects renders it already out of date.

A Textbook of Neurology. By H. Houston Merritt. (Pp. 746; 181 illustrations and 128 tables. 90*s*.) London: Henry Kimpton. 1955.

"Neurology, a branch of medicine which for many years has been traditionally allied with psychiatry, has in recent years returned more closely to the fold of internal medicine."

With these words Dr. Houston Merritt introduces the reader to this excellent new textbook. In order to conserve space the traditional sections on anatomy and methods of examination have been omitted, and the author has also refrained from writing about the psychoneuroses. Discussions with regard to abstruse neurological problems are avoided.

On the other hand, the author presents a well-expressed, matter-of-fact and up-to-date account of existing knowledge which is profusely illustrated by his own clinical experience. The problems of treatment are handled well, and the reader throughout has the feeling that the author is only recommending methods which he has himself found useful.

The author is keenly interested in the biochemical study of diseases which have been labelled as degenerative or heredo-degenerative, and the new American school of neurology which he is helping to lead may be expected to go from strength to strength as biochemical knowledge develops.

This is perhaps the most useful textbook of neurology written in recent years, and will be specially helpful to British physicians and neurologists for the clear account of Dr. Merritt's experience which they can use to supplement the information to be found in British textbooks.

Neurology, 2nd ed. By Kinnier Wilson. Edited by A. Ninian Bruce. (Pp. xxix + 2,060 + index; over 300 illustrations. £10 10*s*. the set.; £3 3s. per vol.) London: Butterworth. 1954.

Dr. Kinnier Wilson's *Neurology* was incomplete at the time of his untimely death, and was published in 1940 in an incomplete form under the editorship of Dr. Ninian Bruce. In this second edition a noteworthy attempt to fill the gaps in the first edition is provided by an excellent chapter by Sir Russell Brain on aphasia, apraxia, and agnosia.

Apart from this important addition, however, the second edition is to a great extent a reprinting of the first edition, while as the editor writes "endeavour has been made to include summaries of the more important neurological advances together with the corresponding references without in any way interfering with the general character of the book". The result is in many respects unfortunate, for it is impossible to bring a section up to date by simply adding a paragraph to what was written nearly 20 years ago: it would surely have been better just to reprint the first edition which contains many fine sections which all are glad to refer to from time to time.

Thus we still read on page 20 that the course of leptomeningitis is "an acute beginning . . . as a rule followed in turn by depression and paralysis . . . inanition hastens death", though treatment with sulphonamides is described a few pages later. On page 84 no attempt has been made to make the discussion of post-exanthematous encephalopathies up to date. Such comments may be made with regard to so many sections in the book that one can only conclude that the editor intended this to be a reprint of the first edition but was persuaded to add a little to each section to enable it to be called a second edition. Thus the long lists of references are concerned almost entirely with papers written before 1940.

What Dr. Kinnier Wilson would have thought of all this is doubtful, for no one was more anxious to be ahead of current thought on neurological problems.

Diseases of the Nervous System. 8th ed. By F. M. R. Walshe. (Pp. xvi + 357; 58 figures. 24*s*.) Edinburgh and London: E. & S. Livingstone. 1955.

This book is evidently popular with students and practitioners, as this is the eighth edition to appear since its first publication in 1940. It deserves the wide audience it will continue to have. It is reminiscent in some ways of Lewis's *Diseases of the Heart*: both are relatively small books for their subject, both may give at first glance a misleading impression of omitting more than a little relevant matter, but in each instance when their views are sought on some particular aspect they will rarely be found to fail in mentioning the relevant facts together with their reasoned interpretation. Diagnosis in neurology lends itself more than in many branches of medicine to a division into site and type of disease process. The author has made use of this in providing a first part to his book on general principles of neurological diagnosis, while in the second and major part a descriptive account of the more common diseases of the nervous system is given. Two minor points of criticism may be mentioned amid the general excellence of the work.

In acute infections of the nervous system pneumococcal meningitis is hardly treated with the urgency it deserves. After a diagnostic lumbar puncture, and sometimes before this on the clinical history alone, the immediate intrathecal injection of antibiotic may be a necessary life-saving procedure. As for epilepsy, there may not be "a hystero-epilepsy", but hysterical patients may have epileptic fits and epileptic patients may be hysterical or otherwise psychiatrically disturbed. Further to confound the doctor in search of a diagnosis, the electroencephalogram may at times show abnormalities which have heretofore been considered "epileptic" in patients not known to have had unequivocal epileptic attacks, but with clear psychiatric abnormalities. The problem may be more difficult than the author here seems to imply. Apart from its matter, the manner of the book is also to be recommended. The author's well known controversialism is here mellowed into an occasional pungency of phrase by which the point is well taken. If his mastery of language occasionally obscures the

weakness of an argument, this is rarely apparent in the present work. A good wine needs no bush, but neurologists as well as students and practitioners will find this a pleasing and useful résumé of their subject.

Clinical Neurology (In Three Volumes). Edited by A. B. Baker. (Pp. 2,023 ; illustrated. 20 gns. the set.) London : Cassell. 1955.

The appearance of this encyclopaedic work is an important occasion and reflects the resurgence of clinical neurology in the U.S.A. There are 65 contributors, and many of the chapters give an excellent account of current knowledge. Some repetition is inevitable, and omissions can always be found in such a compilation. As an example, one may refer to the 70 pages devoted to ophthalmological diagnostic methods. Here many diseases are referred to at length while some well-known neurological phenomena are neglected, such as the internuclear ocular palsies, defects of attention and localization in the visual fields, and the characteristic perimetric findings in wounds of the calcarine cortex. Other conditions which find scant attention are Wernicke's encephalopathy and the neuropathies associated with bronchial carcinoma.

Perhaps the most serious general criticism of this work, however, is the neglect of many of the wider aspects of treatment. This is traditional to many neurological textbooks in the past, but is hardly appropriate to modern expectations. Thus the treatment of epilepsy described refers to anticonvulsants and surgery, but neglects the all-important handling of the patient and planning of his life. Similarly, in the handling of the chronic case of disseminated sclerosis the reader will get no help from this work. No wonder the special associations for various diseases find there is so much for them to do ! There is a chapter on " Neurologic Rehabilitation " which is excellent as far as it goes, but does not adequately fill the general lack of interest in the wider aspects of treatment. The recommended treatment for recovering head injuries (page 1004) will read strangely to British neurologists who have adopted the much more positive attitude towards rehabilitation developed by the war-time head injury centres.

However it is not only in the U.S.A. that neurologists neglect the treatment of their patients, and in other regards this important publication will be much referred to by neurologists. Dr. A. B. Baker is to be congratulated on the publication of these volumes.

The Clinical Examination of the Nervous System. 10th edition. By G. H. Monrad-Krohn. (Pp. xx + 428; 165 figures. 36*s*.) London : H. K. Lewis. 1954.

This tenth edition of a well established book continues to give a very full and satisfactory account of the routine examination of the nervous system. The autonomic system is treated more fully than is usual in this country, and pharmacological tests that can be usefully employed are given.

A modified Binet-Simon test for intelligence is included, although this is now generally outmoded, while simple tests that are commonly used for orientation, awareness, memory, are not mentioned.

It is doubtful if neuroradiology should now be contained within a volume on the examination of the nervous system, though the 70-odd pages devoted to it certainly contain useful information. In later editions it might be worth pruning some of the material which is now largely of historical interest to make room for fuller treatment of electrical diagnosis, and for the methods of examining the interesting syndromes of the posterior parietal lobe.

The Visual Fields. By Brodie Hughes. (Pp. ix + 174 ; 158 figures. 35*s*.) Oxford : Blackwell Scientific Publications. 1954.

This book on visual fields will be widely welcomed, for recent books on this subject are few, and it is especially valuable to have a book written from the neurologist's viewpoint. It is explicitly a statement of the author's personal views and experience, and though references are given at the end of each chapter no attempt is made to survey the literature extensively. The visual fields illustrated, of which there are an admirably large number, are well chosen and have all been charted by the author in person. After describing his technique of quantitative perimetry the author describes first the anatomy of the visual pathways and then the way in which various pathological states affect them.

The fast-moving missiles of modern war can inflict well localized injury to the brain which more closely simulates experimental lesions in an animal than any other type of human pathology. It is therefore surprising that Mr. Hughes does not make use of this valuable material, and it is partly for this reason that his account of the visual radiations and the striate cortex lacks the detail and clarity with which the more anterior visual pathways are described.

The book is refreshingly slim, but in some instances more clinical details would be acceptable. Fig. 65, for instance, shows a visual field attributed to thrombosis of the posterior calcarine artery supplying the depths of the sulcus. The type of field defect shown is rare but has been reported in a lesion of the anterior part of the radiation. The reader is curious to know how the site of this small vascular accident was determined, and his curiosity is increased when he finds the same figure subsequently referred to (p. 142) as due to a lesion of the radiations.

The Pyramidal Tract. By Arthur M. Lassek. (Pp. v + 167. 34*s*.) Springfield, Illinois : Charles C. Thomas. 1954.

This is an interesting and thoughtful book. Professor Lassek here reviews the anatomical, physiological, and clinical facts that have been accumulated about the pyramidal tract mainly during the past century ; though he also mentions earlier views put forward since the French physician, Petit, in 1710 clearly demonstrated the pyramidal decussation in the medulla. The author is well qualified for his task, as he has been contributing to our knowledge of this subject for over 25 years, and

it was he who originally showed by cell and fibre counts that the giant pyramidal cells so prominent in the fifth layer of the motor cortex could account for only a small proportion of the fibres in the medullary pyramid. Although the Betz cells are still held to be largely responsible for the excitable properties of the motor area, and injury limited to the pyramidal tracts produces retrograde degeneration almost exclusively in these cells, nevertheless the fibre components of the tract are almost thirty times more numerous than the Betz cells and are mostly of much smaller diameter than fibres known to be derived from these cells. Moreover, many cases of cerebral palsy show little or no neuronal loss in this tract. There is still a tendency in clinical neurology to emphasize the origin of the tract in the motor area and to imply that this is its main source. Such a view is not supported by the evidence, and indeed earlier workers, such as Ferrier, investigating representation of movement, clearly believed that the pyramidal tract derived from both post- and pre-central gyri. The author's own view is that pyramidal neurons should be regarded as internuncial in function, in which he claims the support of Sherrington. Incidentally, in discussing Babinski's sign he points out the wealth of evidence that it can at times occur in the absence of any pyramidal fibre destruction and casts doubt on its clinical value as a pathognomonic finding. He believes that from the broad viewpoint the function of this tract, so far from being clearly understood, " constitutes an enigmatic and challenging pathway ". Although the assessment of clinical findings is at times uncritical, the facts put forward and the wider views on the anatomical background of motor behaviour are interesting and salutary for the practising neurologist.

Pituitary Chromophobe Adenomas (Neurology Metabolism, Therapy). By John I. Nurnberger and Saul R. Korey. (Pp. 282; 31 figures. 55*s.*; $7.00.) New York: Springer Publishing Co. Inc.; London: Lange, Maxwell & Springer. 1953.

This book describes the clinical and pathological features of chromophobe adenoma of the pituitary, and special attention is paid to those aspects which impinge on general medicine, particularly the disorders of endocrine function. The anatomy and physiology of the hypophysis and of the sella and perisellar region are reviewed. The authors describe 117 cases with neurological, endocrinological, and other investigations, and outline the therapeutic approach suggested by their experience, The book is dedicated to " the rapprochement of neurology to general medicine ", and clearly endocrinologists and neurologists might fruitfully cooperate in this field.

The authors recommend *x*-ray treatment and consider surgery should mainly be employed when radiotherapy fails. At first a course totalling 2,400 r. was given, but now a course of 3,000 r. is recommended and many European authorities would be more ready to accept this suggestion if it was certain that late radiation necrosis did not occur. Unfortunately it is not easy to discover how long the authors' cases have been followed.

The Management of Acute Poliomyelitis. By C. P. Stott and M. Fischer-Williams. (Pp. xii + 99; 43 illustrations. 12*s.* 6*d.*) Edinburgh and London: E. & S. Livingstone. 1955.

Those who have had to treat poliomyelitis in the acute stage will appreciate how much the experienced nurse contributes not only to the comfort and functional recovery of the patient but also to the preservation of life. The incidence of poliomyelitis is so variable both in time and place that, except in a very few centres, it is impossible to maintain a fully experienced nursing staff constantly in being. This small book is well written and incorporates the practical lessons learned by the authors in treating acute poliomyelitis in England and the United States. It deals clearly, amongst other things, with the technique of artificial respiration in tank respirators and by intermittent positive pressure, the value and methods of passive movements to the limbs, and the use and abuse of hot packs.

Die Ursachen der Kinderlahmung und Verwandter Krankheitszustande. By E. R. Elste. (Pp. 148.) Emmendingen: Senior Verlag. 1954.

This book consists chiefly of a review of world literature regarding neurotropic viruses and their epidemiological behaviour. There is special reference to the recent literature regarding poliomyelitis.

Proceedings of the Third Medical Conference of Muscular Dystrophy Association of America, Inc. Edited by H. D. Bouman. (Pp. 324. No price.) New York. 1955.

These papers were presented in October, 1954, and contain many important reports on the present-day knowledge of the chemistry, physiology, and pharmacology of muscle in health and disease.

Die Cervikalen Vertebral-Syndrome. Edited by F. Reischauer. (Pp. 71; illustrated. DM. 7.80.) Stuttgart: Georg Thieme Verlag. 1955.

This booklet is a collection of papers and discussions by various authors given at a surgical meeting in 1954 and is concerned with the clinical syndromes resulting from or associated with cervical spondylosis or, as it is also called, cervical osteochondrosis. The book reveals not only the complexity of the problem but also the confusion which still exists among the authors regarding its analysis and interpretation. There is a tendency on the part of the majority of the authors to turn away from the conception of mechanical compression of the spinal root by the bony alterations as the main or even the only cause of the irritative symptoms. The following, more comprehensive, papers need special mention :—

Kuhlendahl and others discuss those cases of cervical spondylosis associated with spinal cord symptoms. The involvement of the pyramidal tract and a more or less marked damage of the spino-thalamic tracts, were the predominant symptoms, while posterior column symptoms were rare. The authors accept the view that circulatory disturbances in the distribution of the

anterior spinal artery, due to compression by disc protrusions, cause the myelopathy.

The authors consider the spinal cord changes as irreversible, but they believe that further progression can be prevented by the operation. Tönnis and Krenkel report their experience with surgical treatment in 61 cases, between 1951 and 1954. The authors distinguish osteochondrosis, in which the operation was successful in only 26·5% cases, from lateral prolapsed intervertebral disc with 50% good results and medial prolapsed intervetrebral disc with only 20% good results. They consider that immediate operation is indicated for the medial prolapsed intervertebral disc, but they also advise operation for the other two groups, if conservative treatment has proved unsuccessful.

In contrast to these authors, Reischauer, the editor of this booklet and himself a general surgeon, passionately advocates conservative treatment of cervical vertebral syndromes. In rejecting mechanical compression as the decisive factor in the aetiology of the cervical irritative syndromes, he considers a "neural hyperergic" reaction of the spinal roots as the essential factor, and he emphasizes that this reaction can be abolished pharmacologically without the anatomical situation being changed. His favourite method of treatment, apart from the psychological approach, is procaine block of the stellate ganglion. Reischauer claims that he was the first to make the German doctor aware of the existence, clinical picture, and special entity of the cervical root irritation syndrome, and—as he expresses it—in accordance with the tradition of true German medical teaching, he has dissociated himself from the purely mechanical conception of the mechanism of the syndrome held in foreign countries which has led to a surgical-orthopaedic line of treatment. He deplores that that foreign influence, alien to German nature, has been accepted so widely amongst his German colleagues!

Die Chirurgie der Peripheren Nerven (The Surgery of Peripheral Nerves). By Henry Nigst. (Pp. viii + 196; 104 figures. DM. 29.70). Stuttgart: Georg Thieme Verlag. 1955.

It is the author's aim to give, in this monograph, a brief but comprehensive survey of the advances made during World War II in the surgical treatment of peripheral nerve lesions. The survey is based mainly on the experience of workers in this field in the English-speaking countries, and, as the author studied after the war under Mr. Seddon, it is natural that the observations of the team of the Oxford Peripheral Nerve Centre have a prominent place in this survey.

In the general part of the book, following an historical introduction, a brief analysis is given of the functional changes resulting from peripheral nerve lesions and of their diagnosis by various clinical methods, amongst which the author emphasizes the value of sweat tests for the clarification of peripheral nerve lesions. In describing various dye tests, the author makes incorrect reference to the colour indicators used for the sweat tests: the colour indicator of the starch iodine method is not black but dark blue, and the colour of the quinizarin powder is not crimson ("purpurrot") but purple—obviously the author confused these words when translating from the English into German.

In a special chapter, the author discusses in detail the pathological changes underlying the degeneration and regeneration of peripheral nerves in correlation to the indications for surgical treatment. This is followed by a description of the general surgical techniques, including after-care following nerve suture. After discussing the special features of peripheral nerve lesions, combined with fractures and vascular lesions, and the problem of pain following peripheral nerve injuries, technical details of the surgical treatment of lesions of individual nerves are described and illustrated by instructive drawings and photographs.

Continental surgeons unfamiliar with the advances made in recent years in the English-speaking countries in the treatment of peripheral nerve lesions will find this monograph a useful guide.

Clinical Neurosurgery. Proceedings of the Congress of Neurological Surgeons. Volume I. (Pp. viii + 202; 89 figures. 61*s.* 6*d.*) London: Baillière, Tindall & Cox. 1955.

This is the initial endeavour to present some record of the Congress of Neurological Surgeons. It is proposed that at each annual meeting, in addition to reporting the discussions, one or more neurological scientists will be honoured. In this instance, Sir Geoffrey Jefferson was the person chosen, and the first half of this book contains three noteworthy papers which he gave in the U.S.A., the subjects being "Integration of the Brain", "Trigeminal Neurinomas", and "Compression of the Optic Pathways by Aneurysms". There follows a report of three panel discussions on "the Frontal Lobes", "Psychosurgery", and the "Use of Fluids and Electrolytes in the Management of the Neurosurgical Patient".

Pain: Its Mechanisms and Neurosurgical Control. By James C. White and William H. Sweet. (Pp. xxiv + 736; 134 illustrations. £6 6*s.*) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1955.

This book is primarily intended for neurosurgeons. The sections on the mechanism of pain are concerned much more with anatomy than physiology, and thus lack something which is nowadays expected from research workers in this field, but the surgical sections contain a great wealth of clinical material of great value to the surgeon. Indeed, there are 420 case histories reported in which the patient has been treated surgically for intractable pain, and a great variety of operations are described. One is somewhat overwhelmed by the surgical view that pain should be treated by cutting something: either the peripheral nerve, the posterior nerve roots, the sympathetic supply, spinothalamic tract, or frontal lobe connexions.

Thus, the cautious doctor will be disturbed to read on page 420 of several patients between 20 and 35 years of age who have had major operations of spinal tractotomy

or rhizotomy for relief of the discomfort of a painful operation scar. Many of the surgical methods described are reported to have failed completely in a high proportion of the cases, so much so that one can hardly be impressed by the clinical approach described. However, the dangers and complications are fully documented with complete frankness, so the reader can calculate for himself the chances of benefit from the various operations considered.

The Abnormal Pneumoencephalogram, 2nd ed. By Leo M. Davidoff and Bernard S. Epstein (Pp. 518; 696 illustrations on 291 figures. 110*s*.) London: Henry Kimpton. 1955.

This is a book of importance in which radiology, clinical signs, and pathological anatomy are considered together. It is welcome among the reference works in all departments where neuroradiology is practised, and the ssue of a second edition provides a fresh opportunity to obtain it for those purposes. It is, however, unlikely to obtain a wider public or to be put to very active use, for more than half the book is devoted to illustrating the ventriculographic appearance of space-occupying lesions which, in many clinics, would today be investigated by angiography.

To those radiologists who have been influenced by modern Swedish teaching, some of the methods here described will appear to be old-fashioned.

One of the features which most clearly "dates" this book is the failure to utilize or to discuss "fractional" lumbar encephalography. On page 29 the authors mention, in passing, that the scout films taken after 20 ml. of helium have been injected are often extremely helpful, but it is clear that they rely upon more extensive gas injections. The loss is theirs, for failure to examine the basal cisterns after the controlled injection of air deprives them of the opportunity to illustrate the usefulness of this technique in studying small lesions of the suprasellar region, or the cerebellopontine angle, and in demonstrating the site of obstruction in some cases of external hydrocephalus.

Hyperostosis Cranii. By Sherwood Moore. (Pp. xxii + 226; 107 figures. 75*s*.) Oxford: Blackwell Scientific Publications; Springfield, Illinois: Charles C. Thomas. 1955.

The author has conducted an extensive review of skull radiographs and presents much data on the measurements of normal and abnormal skulls. The book, however, is primarily concerned with the syndrome associated with the names of Morgagni, Morel, Stewart, and Moore. The author is an ardent believer in this syndrome, but among the many who are sceptical of the syndrome's existence this book will make few converts.

Physiologie du Système Nerveux Central, 2nd ed. By Georges Morin. (Pp. 354; 95 illustrations. Fr.frs. 2,300.–) Paris: Masson et Cie. 1955.

In 344 pages, Professor Morin has produced an account of the physiology of the central nervous system for medical students. He presents without irrelevant detail an historical sequence of important discoveries, ideas, clinical observations, and laboratory experiments leading to modern knowledge. The subject matter is comprehensive—from spinal roots to cerebral cortex—but the division of chapters is unbalanced and their order original, if irrational.

In parts, the book is out of date. Lloyd's important work on the spinal cord and reflexes receives but scant mention and Eccles' none at all. Though the subject of "muscle tone" has a whole chapter devoted to it, the vastly important muscle spindle is dismissed in a few lines.

In general, however, this book provides a clear and concise account of the physiology of the central nervous system from the experimental and clinical angle.

Die Occipito-Cervical-Gegend. Eine Diagnostisch-Pathogenetische Studie. By Dr. J. E. W. Brocher. (Pp. x + 145; 91 figures. DM. 48.–.) Stuttgart: Georg Thieme Verlag. 1955.

In the general chapters of this monograph the author describes the anatomical and embryological, as well as the mechanical, peculiarities of the occipito-cervical region and also gives details of the technique of radiological examination of this area.

In the following chapters, the pathology is discussed, with special reference to congenital anomalies of both the occipital bone and the atlas-epistropheus complex.

The monograph is well illustrated.

The Human Brain in Sagittal Section. By Marcus Singer and Paul I. Yakovlev. (Pp. v + 81; 46 illustrations. 45*s*.) Oxford: Blackwell Scientific Publications. 1955.

This atlas is undoubtedly useful, for relatively little has been published describing the human brain in sagittal section. While for many purposes coronal sections through the cerebral hemispheres and horizontal sections through the brain-stem are the most convenient material to work on, there are occasions when the sagittal plane is of especial value, and some help in understanding such preparations will be found in these illustrations.

The sections are taken from a whole brain embedded in celloidin and the 45 plates shown are stained by a method for myelin. Most sections are magnified 1·5 times, whilst 16 plates showing the brain-stem are enlarged 2·5 times to give greater detail.

Although this work can in no way be compared with the monumental and indispensable atlas of Riley, it can be recommended as a very useful addition to the library of the anatomist, neurologist, and neuropathologist.

Textbook of the Nervous System. By H. Chandler Elliott, 2nd ed. (Pp. 437; 153 figures, 50 plates. 72*s*.) London: J. B. Lippincott. 1954.

This introductory textbook can be confidently recommended to the student of neurology. The author has a special talent for clarity of arrangement and expression,

and leads the reader by well chosen stages all the way from the neurophysiology of the amoeba to the study of what is known of the human nervous system. He succeeds to an unusual extent in presenting the romance of what is known and the challenge of what is still obscure. However, this second edition is not so up to date as was the first, and there is much recent work, for example, on the olfactory connexions, the higher visual cortex, and the hippocampus, which is not referred to here. Perhaps the author considers these matters too technical for the junior student who must pass an examination in anatomy. If so, many would wish that he would use his talent for description and comment to write a book for the clinical neurologist and psychiatrist, who has no further examinations to worry about !

Genetics and the Inheritance of Integrated Neurological and Psychiatric Patterns. Volume xxxiii of the Research Publications of the Association for Research in Nervous and Mental Disease. Edited by Davenport Hooker and Clarence C. Hare. (Pp. xiv + 426 ; 77 illustrations. 76*s*. 6*d*.) London : Baillière, Tindall & Cox. 1954.

This book presents the papers read at the thirty-third Annual Meeting of the Association for Research in Nervous and Mental Disease, together with a synopsis of the discussion which followed each paper. The field covered is very large and rather heterogeneous, so that there is very little in the way of a thread of continuity to bind the whole together. The papers themselves vary equally widely in their nature and significance. A large part of them are either essays of a rather general kind, or critical reviews of the literature on the subject chosen ; but there are also contributions of original data.

It is these latter which will have the most permanent value. They include accounts of chemical experiments with strains of mice susceptible to sound-induced seizures (Ginsburg), genetical studies on resistance to viruses (Sabin), reflex activity in the human embryo (Hooker), behavioural growth patterns in foetus and infant (Gesell), studies of the trigeminal nerve and its central connexions in the foetus (Humphrey), the phylogeny of the sensory trigeminal complex (Crosby and Ross), new data on inheritance in phenyl-pyruvic oligophrenia (Jervis), in neuromuscular disease (Tyler), in epilepsy (Lennox and Jolly), and in migraine (Goodell, Lewontin, and Wolff). Apart from the geneticist therefore, there is matter to interest the human and the comparative anatomist, embryologist, physiologist, bacteriologist, biochemist, psychologist, paediatrician, neurologist, and psychiatrist. Of all these, it is the neurologist who draws the biggest dividend.

Personality Changes following Frontal Leucotomy. By P. M. Tow. (Pp. xv + 262 ; 27 figures. 35*s*.) London : Oxford University Press. 1955.

This book is primarily a review of the mental changes after leucotomy in 36 patients personally studied by the author. They were carefully selected from a much larger group, as being substantially " normal " for the psychological tests which were to be applied. The attributes tested were intelligence, vocabulary, tempo (rate of performance), persistence, speed-accuracy preference, perseveration, fluency, use of abstract words, object-sorting, foresight and planning (as shown by Porteus' maze tests), work and pleasure attitudes, and imaginative response (as shown by the ink-blot test). The author found significant reductions in abstract thought, in planning, foresight, and appreciation of one's own mistakes. Relations and differences were also less easily appreciated. Surprisingly, however, persistence, speed-accuracy, and perseveration did not show much change, although the author gained the impression that sustained attention is impaired. The changes mentioned are in cognitive functions, but the author is quite aware that underlying motivational changes (which are themselves not easily assessed quantitatively but which general observations suggest certainly occur) may in fact be causing apparent intellectual changes. The value of this book lies particularly in its attempt at personal assessment of all cases by quantitative methods where possible. For the clinician its usefulness is increased by the follow-up of cases for several years after operation. In addition, the first nine chapters contain a brief but critical assessment of earlier work on frontal lobe function in both its clinical and experimental aspects.

Psychosurgery and the Self. By Mary F. Robinson and Walter Freeman. (Pp. ix + 118. $3.00.) New York : Grune & Stratton. 1954.

The subjects of this study were 77 patients who had had a cerebral lobotomy, and 17 patients who had recovered from a mental illness without any such operation. The inquiry was designed to test the hypothesis that the operation " alters the structure of the self through reducing capacity for the feeling of self-continuity ". Three controlled interview techniques were used, which were intended to measure self-regarding span, self-concern, and sensibility. Patients who had had a standard prefrontal lobotomy differed from the control subjects in their performance on these tests, and when very small groups of patients who had had transorbital or other variants of the operation were compared with one another and with the standard group it appeared that the test scores varied with the degree of brain damage sustained. The findings are suggestive rather than conclusive. The weakness of the inquiry lies in the technical handling of the tests, which have not been standardized on a normal population, or validated, and are scored in an unsatisfactory way. The control group used in the study was dangerously small.

Études Psychiatriques ; Structure des Psychoses Aigues et Destructuration de la Conscience. By Henri Ey. (Pp. 787. Price not given) Paris : Desclee de Brouwer et Cie. 1954.

Twenty years ago the publication of a little green book on *Hallucinations et Délire* indicated to the discriminating reader that a well-informed and penetrating mind had come into French psychiatry. Dr. Ey, the

author of the book, had already published a thesis on the chemical concomitants of morbid emotional states and several papers on hallucinations and kindred topics, but these were hardly attended to outside France. Clarity and precision, the qualities which M. Séglas praised in his foreword to the book on hallucinations and delusions, have continued to characterize M. Ey's writings, and are prominent in the magnum opus which has been appearing volume by volume since 1950. The present book, the third in the series, is written on the same plan as its predecessors and displays M. Ey's extraordinarily wide acquaintance with psychiatric writings in many languages—a rare feature nowadays—and his catholic yet critical interest in diverse expositions and theories.

The acute psychoses, with which this volume is concerned, raise problems of classification. The first chapter in the book elucidates the history of this complicated question and explains the author's principles of classification. In succeeding chapters mania, melancholia, atypical acute hallucinoses and delusional attacks, confusion and oneiroid states, cyclical affective disorders, and epilepsy are examined. The philosophical and psychological problems inherent in the author's theory of consciousness and its hierarchical breakdown are lucidly stated in the final chapter, which is crucial for the author's purpose. It is not easy reading, nor does it accord with the current English view of consciousness, but it contains material for a basic approach to the psychopathology of mental disorder. The author has been much influenced by Hughlings Jackson.

This is a learned and thoughtful work, which demonstrates that French psychiatry, with its great tradition, still offers an original viewpoint and a vigorous contribution of its own, deserving of our close attention.

The Six Schizophrenias—Reaction Patterns in Children and Adults. By Samuel J. Beck; with a Clinical Introduction by Roy R. Grinker, and a chapter concerning Q-methodology by Professor William Stephenson. Research Monographs—No. 6. (Pp. 238. $5.) New York: American Orthopsychiatric Association. 1954.

The author's experience in the use and interpretation of the Rorschach test ensures that this part of the joint enquiry reported here was very competently performed. The Rorschach studies, however, were not the most important and difficult part of the research. This lay in finding a *point de repère*. Since schizophrenia was the subject of investigation, some consistency of definition and uniformity in its application were obviously essential, yet were lacking. The investigators held strongly to the dynamic conception of mental illness and deprecated the use of the Kraepelinian concepts. In an illuminating discussion reported verbatim in the book, Dr. Grinker (who directed the psychiatric procedures) said that the investigators must forget all the statements about schizophrenia "in Bleuler and any of the other textbooks" and must begin afresh. The method employed consisted in taking series of persons diagnosed as schizophrenic, assessing them in respect of a large number of psychiatric and Rorschach items believed to be appropriate to schizophrenia, and then, for each person, carrying out a factorial analysis of these items with a view to establishing clinical and psychological patterns. Six such patterns or reaction types were arrived at and are here described. They are of interest because of the route by which they were reached rather than for any intrinsic novelty or promise they contain of a more objective and communicable set of criteria for diagnosing schizophrenia in children or adults.

The Self in Psychotic Process: Its Symbolization in Schizophrenia. By J. W. Perry; with a Foreword by C. G. Jung. (Pp. 184; 16 figures. 37*s.* 6*d.*) London: Cambridge University Press. 1954.

Apart from the writings of Jung himself, little medical literature has been published on the psychopathology of mental illness interpreted according to the Jungian method and theory. The present book contains observations made by the author during nine weeks' treatment of a woman who previously and subsequently received electro-convulsive therapy for her schizophrenic attack, from which she recovered after about nine months' illness.

Twelve coloured drawings which the patient produced at Dr. Perry's request are the main material; they are related to her delusions and total mental state, and their symbolism is closely scrutinized. The quadrated circle, familiar as a symbol in many religions, was very prominent in the drawings, and the patient showed much concern about her position at the centre of the circle of her family and her friends. Dr. Perry examines the relation of this to the archetypal images which Jung considered so important, and expounds the theoretical matrix, paying particular attention to the symbolism of opposites and of rebirth. The book is well written and impressively erudite; it offers a faithful presentation of the standpoint of analytical psychology; and it will be attractive to readers in direct ratio to their enjoyment of studies in abstruse symbolism, whether mystical, psychological, or alchemical.

La Therapeutique par le Sommeil. By J.-M. Angel, with the collaboration of Francis Peillet; Preface by P. P. Wertheimer. (Pp. 152. Fr. frs. 820.–.) Paris: Masson et Cie. 1953.

Although Dr. Angel is a psychiatrist, his account of continuous sleep therapy shows much misconception of the history of this method of psychiatric treatment. Possibly this is because he took up the method at the instance of a surgeon, Professor Wertheimer of Lyons, who had heard of its use in Russia and wished it to be applied in his wards. French psychiatrists mostly disregarded the method at the time (in the 1920s and 30s) when it was being extensively employed in Switzerland and Great Britain. Dr. Angel believes that it was first used in Russia after the second world war; this is incorrect, as the writings of Serejski, Ivanov-Smolenski, Richter and Stefanov, Shevelev and others from 1935 onwards attest. Dr. Angel gives a lucid account of the Russian views about the rationale of the method, which of course relies exclusively on Pavlov's theories of

inhibition ; and he outlines the technique and contra-indications. He makes unduly light of the dangers, though in a footnote he says that one of his patients, a hypertensive, died " *au cours d'une cure* ". The treatment has been applied in neurotic and psychotic disorders, arterial hypertension, peptic ulcer, asthma, eczema, psoriasis, neurodermatitis, post-operative shock, head injury, and a variety of other conditions. Evidently in France it is a running mate for artificial " hibernation " produced by chlorpromazine, which is likewise supposed by Follin to have an inhibiting effect on the cerebral cortex : Dr. Angel evidently favours a combination of the two methods.

The Lowenfeld Mosaic Test. By Margaret Lowenfeld. (Pp. 300 ; 144 coloured plates, 15 figures. 50*s*.) London : Newman Neame. 1954.

This book describes the mosaic test of personality devised and used by the author, and includes a description of the responses to the material by individuals of different age, culture-pattern, and mental stability.

To a certain group of psychologists its chief interest will probably lie in the possibility it offers of distinguishing between normal and abnormal mental states ; to anthropologists it may prove a useful tool for comparing the art-forms of different cultures ; to artists the 144 coloured plates may have a certain fascination.

The author herself is at pains to point out the value of this test compared with others of personality and intellect, and in so doing unconsciously draws attention to a defect in most mental tests, her own included—they are not really tests at all. This one, like others in the repertoire of the clinical psychologist, aims to test no particular hypothesis, and although each mosaic designed by an individual obviously reflects his attitudes and abilities, its interpretations, as the author points out, depend on a wide experience of human behaviour.

Induced Abortion on Psychiatric Grounds. By Martin Ekblad. (Pp. 237.) Copenhagen : Acta Psychiatrica Neurologica Scandinavica Supplementum 99. 1955.

This well-written monograph is specially relevant to social psychiatry. It is primarily an account of psychiatric follow-up studies of 479 women, upon whom legally authorized abortions were carried out in Stockholm. It includes a concise account of the medico-legal history of this procedure in Sweden, and statistics about it from 1939 to 1952.

BOOKS RECEIVED

(Review in a later issue is not precluded by notice here of books recently received.)

Histopathologie und Klinische Symptomatologie der Anoxisch-Vasalen Hirnschädigungen. By S. Környey. (Pp. 239 ; 89 figures. Price not given.) Budapest : Akádemiai Kiadó. 1955.

Alcohol and Alcoholism. Report of an Expert Committee : W.H.O. Technical Report Series No. 94. (Pp. 14. 1*s*. 9*d*.) Geneva : World Health Organization ; London : H.M. Stationery Office. 1955.

Die Zerebralen Herdstörungen bei Hinterhauptsverletzungen und ihre Beurteilung. By Clemens Faust. (Pp. viii + 111 ; 41 figures. DM. 14.70.) Stuttgart : Georg Thieme Verlag. 1955.

The Psychology of Abnormal People. By John J. B. Morgan and George D. Lovell. Revised edition. (Pp. xi + 688 ; illustrated. 35*s*.) London : Longmans, Green.

Psychiatry for the Family Physician. By C. Knight Aldrich. (Pp. ix + 274. 43*s*.) London : McGraw-Hill. 1955.

A Manual of Psychiatry, 3rd ed. By K. R. Stallworthy. (Pp. 324. 30*s*.) Christchurch, N.Z. : N. M. Peryer. 1955.

Legislation Affecting Psychiatric Treatment. Fourth Report of the Expert Committee on Mental Health : W.H.O. Technical Report Series No. 98. (Pp. 25. 1*s*. 9*d*.) Geneva : World Health Organization ; London : H.M. Stationery Office. 1955.

The Postural Complex : Observations as to Cause, Diagnosis and Treatment. By Laurence Jones. (Pp. xvii + 156 ; 79 figures. 70*s*.) Oxford : Blackwell Scientific Publications. 1955.

Atlas of Roentgen Anatomy of the Skull. By Lewis E. Etter. (Pp. xv + 215 ; 237 plates. £5 6*s*.) Oxford : Blackwell Scientific Publications. 1955.

J.A.M.A. Clinical Abstracts of Diagnosis and Treatment. Edited by Noah D. Fabricant. (Pp. vi + 627. $5.50.) London and New York : Grune & Stratton. 1955.

Lehrbuch der Allgemeinen Psychopathologie. By K. W. Bash. (Pp. xvi + 288 ; 10 figures. DM 29.50.) Stuttgart : Georg Thieme Verlag. 1955.

Psychological Medicine. By Desmond Curran and Maurice Partridge. (Pp. viii + 407 ; 20 figures. 21*s*.) Edinburgh and London : E. & S. Livingstone. 1955.

Electrochemistry in Biology and Medicine. Edited by Theodore Shedlovsky. (Pp. xii + 369 ; illustrated. 84*s*.) London : Chapman & Hall ; New York : John Wiley. 1955.

Studies on the Cerebral Cortex. By S. Ramón y Cajal. (Pp. xi + 179 ; 108 figures. 27*s*. 6*d*.) London : Lloyd-Luke. 1955.

Thallium Poisoning. By J. J. G. Prick, M. G. Sillevis Smitt, and L. Muller. (Pp. vi + 155 ; 21 figures. 19*s*.) London : Cleaver-Hume Press. 1955.

The Postnatal Development of the Human Cerebral Cortex. Volume V : **The Cortex of the Fifteen-Month Infant.** By J. LeRoy Conel. (Pp. 220 + 235 figures on 109 plates. 100*s*.) Cambridge, Mass. : Harvard University Press ; London : Oxford University Press (Geoffrey Cumberlege). 1955.

Biochemistry and the Central Nervous System. By Henry McIlwain. (Pp. vii + 272 ; 43 figures. 40*s*.) London : J. & A. Churchill. 1955.

We welcome the appearance of *Neuro-Chirurgie*, a new journal designed to report the transactions of the French-speaking Neurosurgical Society. The first issue appeared in February, 1955.

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